REFERENCE NO.

11

In re application of: Lawrence R. McGee, et al.
Application No.: 10/719,997
Filing Date: November 20, 2003
Attorney Docket No.: 018781-006330US

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 239/94, 239/88, 239/95, 215/44, 409/12, A61K 31/505 — A1

(11) International Publication Number: WO 96/09294

(43) International Publication Date: 28 March 1996 (28.03.96)

(21) International Application Number: PCT/GB95/02202

(22) International Filing Date: 18 September 1995 (18.09.95)

(30) Priority Data:

9418852.1	19 September 1994 (19.09.94)	GB
9507788.9	13 April 1995 (13.04.95)	GB
9510757.9	26 May 1995 (26.05.95)	GB

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(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SUBSTITUTED HETEROAROMATIC COMPOUNDS AND THEIR USE IN MEDICINE

(57) Abstract

The invention is directed towards substituted heteroaromatic compounds which are protein tyrosine kinase inhibitors, in particular substituted quinolines and quinazolines. Methods of their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of psoriasis, fibrosis, atherosclerosis, restenosis, auto-immune disease, allergy, asthma, transplantation rejection, inflammation, thrombosis, nervous system diseases, and cancer.

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SUBSTITUTED HETEROAROMATIC COMPOUNDS AND THEIR USE IN MEDICINE

The present invention relates to a series of substituted heteroaromatic compounds, methods for their preparation, pharmaceutical compositions containing them and their use in medicine. In particular, the invention relates to quinoline and quinazoline derivatives which exhibit protein tyrosine kinase inhibition.

Protein protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth and differentiation (A.F.Wilks, Progress in Growth Factor Research, 1990 (2), 97-111). Protein tyrosine kinases can be broadly classified as growth factor receptor (e.g. EGF-R, PDGF-R, FGF-R and c-erbB-2) or non-receptor (e.g. c-src, bcr-abl) kinases. Inappropriate or uncontrolled activation of many of these kinases i.e. aberrant protein tyrosine kinase activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth.

Aberrant activity of protein tyrosine kinases such as c-erbB-2, c-src, p56lck, EGF-R, PDGF-R, and zap70 has been implicated in human malignancies. For example, aberrant EGF-R activity has been implicated in cancers of the head and neck, and aberrant c-erbB-2 activity in breast, ovarian, non-small cell lung, pancreatic, gastric and colon cancers. Inhibitors of protein tyrosine kinase should therefore provide a treatment for tumours such as those outlined above.

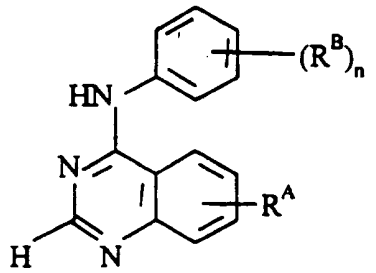
Aberrant protein tyrosine kinase activity has also been implicated in a variety of other disorders: psoriasis, (Dvir et al, J.Cell.Biol; 1991, 113, 857-865), fibrosis, atherosclerosis, restenosis, (Buchdunger et al, Proc.Natl.Acad.Sci. USA; 1991, 92, 2258-2262), auto-immune disease, allergy, asthma, transplantation rejection (Klausner and Samelson, Cell; 1991, 64, 875-878), inflammation (Berkois, Blood; 1992, 79(9), 2446-2454), thrombosis (Salari et al, FEBS; 1990, 263(1), 104-108) and nervous system diseases (Ohmichi et al, Biochemistry, 1992, 31, 4034-4039). Inhibitors of the specific protein tyrosine kinases involved in these diseases eg PDGF-R in restenosis and EGF-R in psoriasis, should lead to novel therapies for such disorders. P56lck and zap 70 are indicated in disease conditions in which T cells are hyperactive eg rheumatoid arthritis, autoimmune disease, allergy, asthma and graft rejection.

Published European Patent numbers 0520722, 0566226, 0602851, 0635498 and 0635507 disclose quinazoline derivatives and their preparation for use in the treatment

of cancer. The above citations note that receptor tyrosine kinases in general, which are important in the transmission of biochemical signals initiating cell replication, are frequently present in common human cancers such as breast cancer (Sainsbury *et al* Brit. J. Cancer 1988, 58, 458). These citations also state that tyrosine kinase activity is rarely detected in normal cells whereas it is frequently detectable in malignant cells (Hunter, Cell, 1987, 50, 823) and it is suggested that inhibitors of receptor tyrosine kinase should be of value as inhibitors of the growth of mammalian cancer cells (Yaish *et al*. Science, 1988, 242, 933). The above citations therefore have the common aim of providing quinazoline derivatives which inhibit receptor tyrosine kinases involved in controlling the tumourigenic phenotype.

Broad spectrum inhibition of protein tyrosine kinase may not provide optimal treatment of the tumour, and could in certain cases even be deterimental to subjects since protein tyrosine kinases provide an essential role in the normal regulation of cell growth.

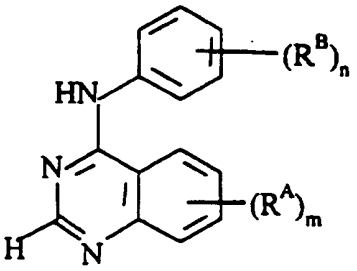
European Patent Application 0520722A discloses a class of quinazoline derivatives having antitumour activity and having the formula (I)



(I)

wherein, for example, R^A is hydrogen, trifluoromethyl or nitro, n is 1 and R^B is halogeno, trifluoromethyl, nitro, cyano, (1-4C)alkyl, (1-4C)alkoxy, N-(1-4C)alkylamino, N,N-di-((1-4C)alkyl)amino, (1-4C)alkylthio, (1-4C)alkylsulphinyl or (1-4C)alkylsulphonyl. These compounds are claimed to be inhibitors of the EGF tyrosine kinase receptor and other unspecified protein tyrosine kinases.

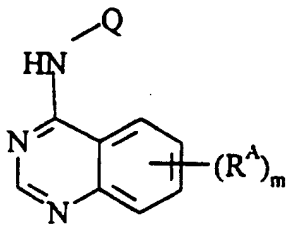
EP 0566 226A discloses quinazoline derivatives of the formula (2):



(2)

wherein m is 1, 2 or 3 and each R^A includes hydroxy, amino, carboxy, carbamoyl, ureido, (1-4C) alkoxycarbonyl, N(1-4C) alkylcarbamoyl, N,N-di[(1-4C)alkyl]carbamoyl, hydroxyamino, (1-4C) alkylamino, (2-4C)alkanoyloxyamino, trifluoromethoxy, (1-4C)alkyl, (1-4C)alkoxy and (1-3C)alkenedioxy; n is 1 or 2 and each R^B includes; hydrogen, hydroxy, halogeno, trifluoromethyl, amino, nitro, cyano and (1-4C) alkyl. The compounds are claimed to be inhibitors of the EGF tyrosine kinase receptor and other unspecified protein tyrosine kinases.

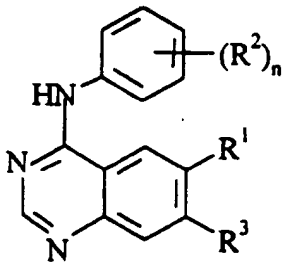
EP0602851 discloses quinazoline derivatives of the formula (3) :



(3)

wherein m is 1, 2 or 3 and each R^A includes hydroxy, amino, ureido, hydroxyamino, trifluoromethoxy, (1-4C)alkyl, (1-4C) alkoxy and (1-3C) alkenedioxy; and Q is a 9 or 10-membered bicyclic heterocyclic moiety containing one or two nitrogen atoms and optionally containing a further heteroatom selected from nitrogen, oxygen or sulphur, or Q is a 9 or 10-membered bicyclic aryl moiety, the heterocyclic or aryl moiety optionally bearing one or two substituents selected from halogeno, hydroxy, oxo, amino, nitro, carbamoyl, (1-4C) alkyl, (1-4C) alkoxy, (1-4C) alkylamino, di-[(1-4C) alkyl]amino and (2-4C) alkanoylamino. The compounds are claimed to be inhibitors of the EGF tyrosine kinase receptor and other unspecified tyrosine kinases.

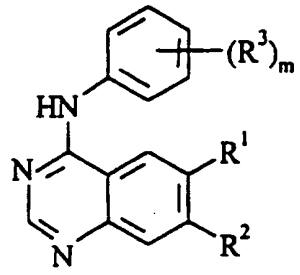
EP0635498 discloses quinazolines of the formula (4),



(4)

wherein R^1 includes hydroxy, amino, hydroxyamino, (1-4C)alkoxy, (1-4C) alkylamino and di-[(1-4C)alkyl]amino; R^2 includes independently hydrogen, hydroxy, halogeno, (1-4C)alkyl, (1-4C)alkoxy or (2-4C) alkanoylamino; n is 1, 2 or 3; and R^3 is halogeno.

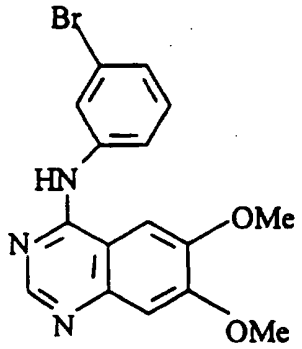
EP0635507 discloses tricyclic derivatives of the formula (5) :



(5)

wherein R^1 and R^2 together form specified optionally substituted groups containing at least one heteroatom so as to form a 5 or 6 membered ring, and R^3 includes independently hydrogen, hydroxy, halogeno, (1-4C)alkyl, (1-4C) alkoxy di-[(1-4C)alkyl]amino, or (2-4C)alkanoylamino.

Selective inhibition of the EGF receptor is, however, disclosed by Fry et al (Science, 265, 1093 (1994)). This citation discloses that the compound of formula:



is a highly selective inhibitor of the EGF receptor tyrosine kinase at picomolar concentrations while inhibiting other tyrosine kinases only at micromolar or higher concentrations.

It is therefore a general object of the present invention to provide compounds suitable for the treatment of disorders mediated by protein tyrosine kinase activity, and in particular treatment of the above mentioned disorders. In addition to the treatment of tumours, the present invention envisages that other disorders mediated by protein

tyrosine kinase activity may be treated effectively by preferential inhibition of the appropriate protein tyrosine kinase activity.

It is another object of the present invention to provide compounds which preferentially inhibit protein tyrosine kinases, such as c-erbB-2, c-src, p56lck, EGF-R, PDGF-R, and zap70 protein tyrosine kinases.

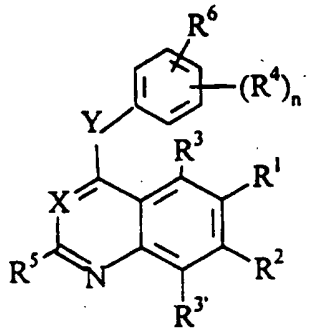
A further object of the present invention is to provide compounds useful in the treatment of protein tyrosine kinase related diseases which minimise undesirable side-effects in the recipient.

The present invention relates to certain quinoline and quinazoline derivatives which may be used to treat disorders mediated by protein tyrosine kinases and in particular have anti-cancer properties. More particularly, the compounds of the present invention are potent inhibitors of protein tyrosine kinases such as c-erbB-2, EGF-R, c-src, p56lck, PDGF, and zap 70 thereby allowing clinical management of particular diseased tissues.

The present invention envisages, in particular, the treatment of human malignancies, for example breast, stomach, ovary, colon, lung and pancreatic tumours, especially those driven by c-erbB-2, using the compounds of the present invention. For example, the invention includes compounds which are highly active against the c-erbB-2 protein tyrosine kinase in preference to the EGF receptor kinase hence allowing treatment of c-erbB-2 driven tumours.

More particularly, the present invention envisages that disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition of the appropriate protein tyrosine kinase activity in a relatively selective manner, thereby minimising potential side effects.

Accordingly, the present invention provides a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof.

wherein X is N or CH;

Y is a group $W(CH_2)$, $(CH_2)W$, or W, in which W is O, $S(O)_m$ wherein m is 0, 1 or 2, or NR^a wherein R^a is hydrogen or a C_{1-8} alkyl group;

R^1, R^2, R^3 and $R^{3'}$ are the same or different and are each selected from the group comprising; amino, hydrogen, halogen, hydroxy, nitro, carboxy, trifluoromethyl, trifluoromethoxy, carbamoyl, ureido, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-8} cycloalkoxyl, C_{4-8} alkylcyclo alkoxy, C_{1-8} alkoxycarbonyl, N-C_{1-4} alkylcarbamoyl, N,N-di-[C_{1-4} alkyl]carbamoyl, hydroxyamino, C_{1-4} alkoxyamino, C_{2-4} alkanoyloxyamino, C_{1-4} alkylamino, di[C_{1-4} alkyl]amino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-C_{1-4} alkylpiperazin-1-yl, C_{1-8} alkylthio, arylthio, C_{1-4} alkylsulphinyl, arylsulphinyl, C_{1-4} alkylsulphonyl, arylsulphonyl, halogeno-C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{2-4} alkanoyloxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4} alkyl, carboxy-C_{1-4} alkyl, C_{1-4}

alkoxycarbonyl-C_{1-4}-alkyl,carbamoyl-C_{1-4} alkyl, N-C_{1-4} alkylcarbamoyl-C_{1-4}alkyl, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4}alkyl, amino-C_{1-4} alkyl, C_{1-4} alkylamino-C_{1-4} alkyl, di-[C_{1-4} alkyl]amino-C_{1-4} alkyl, piperidino-C_{1-4} alkyl, morpholino-C_{1-4} alkyl, piperazin-1-yl-C_{1-4} alkyl, 4-C_{1-4} alkylpiperazin-1-yl-C_{1-4} alkyl, hydroxy-C_{2-4} alkoxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkoxy-C_{1-4} alkyl, hydroxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkylthio-C_{1-4} alkyl, hydroxy-C_{2-4} alkylthio-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylthio-C_{1-4} alkyl, phenoxy-C_{1-4} alkyl, anilino-C_{1-4} alkyl, phenylthio-C_{1-4} alkyl, cyano-C_{1-4} alkyl, halogeno-C_{2-4} alkoxy, hydroxy-C_{2-4} alkoxy, C_{2-4} alkanoyloxy-C_{2-4} alkoxy, C_{1-4} alkoxy-C_{2-4} alkoxy, carboxy-C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl-C_{1-4} alkoxy, carbamoyl-C_{1-4} alkoxy, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkoxy, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkoxy, amino-C_{2-4} alkoxy, C_{1-4} alkylamino-C_{2-4} alkoxy, di-[C_{1-4} alkyl]amino-C_{2-4} alkoxy, C_{2-4} alkanoyloxy, hydroxy-C_{2-4} alkanoyloxy, C_{1-4}alkoxy-C_{2-4} alkanoyloxy, phenyl-C_{1-4} alkoxy, phenoxy-C_{2-4} alkoxy, anilino-C_{2-4} alkoxy, phenylthio-C_{2-4} alkoxy, piperidino-C_{2-4} alkoxy, morpholino-C_{2-4} alkoxy, piperazin-1-yl-C_{2-4} alkoxy, 4-C_{1-4} alkylpiperazin-1-yl-C_{2-4} alkoxy, halogeno-C_{2-4} alkylamino, hydroxy-C_{2-4} alkylamino, C_{2-4} alkanoyloxy-C_{2-4} alkylamino, C_{1-4} alkoxy-C_{2-4} alkylamino, carboxy-C_{1-4} alkylamino, C_{1-4} alkoxycarbonyl-C_{1-4} alkylamino, carbamoyl-C_{1-4} alkylamino, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkylamino, amino-C_{2-4} alkylamino, C_{1-4} alkylamino-C_{2-4} alkylamino, di-[C_{1-4}alkylamino-C_{2-4} alkylamino, phenyl-C_{1-4} alkylamino, phenoxy-C_{2-4} alkylamino, anilino-C_{2-4} alkylamino, phenylthio-C_{2-4} alkylamino, C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonylamino, C_{1-4} alkylsulphonylamino, benzamido, benzenesulphonamido, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, halogeno-C_{2-4} alkanoylamino, hydroxy-C_{2-4} alkanoylamino, C_{1-4} alkoxy-C_{2-4} alkanoylamino, carboxy-C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonyl-C_{2-4} alkanoylamino, carbamoyl-C_{2-4} alkanoylamino, N-C_{1-4} alkylcarbamoyl-C_{2-4} alkanoylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{2-4} alkanoylamino, amino-C_{2-4} alkanoylamino, C_{1-4} alkylamino-C_{2-4} alkanoylamino and di-[C_{1-4} alkyl]amino-C_{2-4} alkanoylamino, and wherein said benzamido or benzenesulphonamido substitutent or any anilino, phenoxy or phenyl group on a R^1 substituent may optionally bear one or two halogeno, C_{1-4} alkyl or C_{1-4} alkoxy substituents;

or R^1 and R^2, R^1 and R^3, or R^2 and $R^{3'}$ together form an optionally substituted methylenedioxy or ethylenedioxy group;

each R^4 is independently selected from the group comprising; hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino, di-[C_{1-4} alkyl]amino, C_{1-4} alkylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbamoyl, di-[C_{1-4} alkyl] carbamoyl, carbamyl, C_{1-4} alkoxycarbonyl, cyano, nitro and trifluoromethyl, and n is 1,2 or 3;

R^5 is selected from the group comprising; hydrogen, halogen, trifluoromethyl, C_{1-4} alkyl and C_{1-4} alkoxy;

R^6 is a group ZR^7 wherein Z is joined to R^7 through a $(CH_2)p$ group in which p is 0, 1 or 2 and Z represents a group $V(CH_2)$, $V(CF_2)$, $(CH_2)V$, $(CF_2)V$, or V in which V is a hydrocarbyl group containing 0,1 or 2 carbon atoms, carbonyl, CH(OH), sulphonamide, amide, O, $S(O)_m$ or NR^b where R^b is hydrogen or R^b is C_{1-4} alkyl;

and R^7 is an optionally substituted C_{3-6} cycloalkyl; or an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety.

or R^6 is a group ZR^7 in which Z is NR^b, and NR^b and R^7 together form an optionally substituted 5, 6, 7, 8, 9 or 10-membered heterocyclic moiety.

In an embodiment, R^1, R^2 and R^3 are each selected from amino, hydrogen, halogen, hydroxy, nitro, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, C_{1-8} alkylsulphinyl, C_{1-8} alkylsulphonyl, C_{1-4} alkylamino, or R^1 and R^2 or R^1 and R^3 together form an optionally substituted methylenedioxy or ethylenedioxy group;
$R^{3'}$ is hydrogen; R^4 is hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, di-[C_{1-4} alkyl]amino, nitro or trifluoromethyl;
R^5 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy or halogen;
Z is oxygen, S or NR^b wherein R^b is hydrogen, or C_{1-4} alkyl, and
R^7 is an optionally substituted 5, 6, 7, 8, 9 or 10 membered-carbocyclic or heterocyclic moiety.

In a further embodiment, R^1, R^2 and R^3 are each selected from; hydroxy, halogen, amino, C_{1-4} alkyl, C_{1-4} alkoxy or together form a methylenedioxy or ethylenedioxy group.

In a further embodiment, R^6 is in the para position with respect to Y.

In a further embodiment, $(R^4)_n$ represents meta substituent(s) with respect to Y, preferably n = 1.

In a further embodiment, X is N.

In a further embodiment, Y is NR^b, $NR^b(CH_2)$, or $(CH_2)NR^b$, preferably Y is NR^b.

In a further embodiment, Z is CH_2, NR^b, $NR^b(CH_2)$, $(CH_2)NR^b$,O, $O(CH_2)$, $O(CF_2)$, $(CH_2)O$, $(CF_2)O$, $S(CH_2)$, or carbonyl; preferably Z is CH_2, NR^b, O, $O(CH_2)$ or $O(CF_2)$.

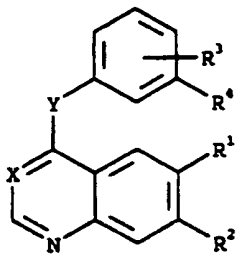
Suitably X is nitrogen.
Suitably Y is a group NR wherein R is hydrogen or methyl, preferably hydrogen.
Suitably Z is oxygen, $O(CH_2)$ or CH_2.
Suitably R^1 and R^2 are independently hydrogen; halogen; C_{1-4} alkyl, such as methyl; or C_{1-4} alkoxy, such as methoxy.
Suitably R^3 and $R^{3'}$ are independently hydrogen, halogen, methyl or methoxy.
Suitably R^4 is hydrogen, halogen or methyl, preferably R^4 is hydrogen.
Suitably R^5 is hydrogen or methyl.
Suitably R^6 is benzyl, phenoxy or benzyloxy.
Preferably R^6 is selected from benzyl, phenoxy or benzyloxy when X is N and Y is NH; or when X is CH and Y is oxygen, S(O)m or NR^a, with R^a preferably being H, wherein m and R^a are as hereinbefore defined.

Suitably R^7 is thiophene or cyclohexane and p is 1 where Z is oxygen

Suitably the 5, 6, 7, 8, 9 or 10- membered heterocyclic moiety is selected from the group comprising: furan, dioxolane, thiophene, pyrrole, imidazole, pyrrolidine, pyran, pyridine, pyrimidine, morpholine, piperidine, oxazoline, oxazolidine, thiazole, thiadiazole, benzofuran, indole, isoindole, quinazoline, quinoline and isoquinoline.

Suitably the 5, 6, 7, 8, 9 or 10- membered carbocyclic moiety is selected from the group comprising: phenyl, benzyl, indene, napthalene, tetralin, decalin, cyclopentyl, cyclohexyl, and cycloheptyl.

In another aspect, the present invention provides a compound of the formula (Ia) :



(Ia)

or a pharmaceutically acceptable salt thereof, wherein X is nitrogen or CH; Y is oxygen, S(O)m wherein m is 0, 1 or 2 or NR wherein R is hydrogen or a C_{1-4} alkyl group; R^1 and R^2 are the same or different and are each selected from hydrogen or C_{1-4} alkoxy; R^3 is a group ZR^6 wherein Z is oxygen, S or NR^a wherein R^a is hydrogen or C_{1-4} alkyl; R^4 is hydrogen, halo, C_{1-4} alkoxy or trifluoromethyl; and R^6 is phenyl or benzyl optionally substituted by one to three halo atoms.

Suitably Y is a group NR wherein R is hydrogen or methyl, preferably hydrogen.

Suitably Z is oxygen.

Suitably R^1 and R^2 are both hydrogen or C_{1-4} alkoxy, such as methoxy.

Suitably R^3 is methoxy, phenoxy or benzyloxy, preferably benzyloxy.

Suitably R^4 is hydrogen, fluorine or trifluoromethyl, preferably R^4 is hydrogen.

In one preferred embodiment of the present invention R^3 is a substituent at the meta or para position of the phenyl ring. Preferably R^3 is selected from phenoxy or benzyloxy when X is N and Y is NH.

Examples of compounds of the present invention include;
4-(3-Phenoxyanilino)quinoline hydrochloride;6,7-Dimethoxy-4-(3-phenoxyanilino)quinoline hydrochloride; 4-(4-Phenoxyanilino)quinoline hydrochloride; 6,7-Dimethoxy-4-(4-phenoxyanilino)quinoline hydrochloride; 4-(3-Benzyloxyanilino)quinoline hydrochloride; 4-(4-Benzyloxyanilino)quinoline hydrochloride; 4-(4-Benzyloxyanilino)-6,7-dimethoxyquinoline hydrochloride; 5-Chloro-2-[2-methyl-4-(4-quinolylamino)phenyl]isoindol-1,3-dione hydrochloride; 5-Chloro-2-[4-(6,7-dimethoxy-4-quinolylamino)-2-methylphenyl]isoindol-1,3-dione hydrochloride; 4-(4-Benzyloxyanilino)-2-methylquinoline hydrochloride; 4-(4-

Phenoxyanilino)-2-methylquinoline hydrochloride; 4-(4-Benzyloxyphenoxy)quinazoline; 4-(4-Benzyloxyphenoxy)-6,7-dimethoxyquinazoline; 4-[(4-Benzylmercapto)phenoxy]quinazoline; 4-[(4-Benzylmercapto)phenoxy]-6,7-dimethoxyquinazoline; 4-(4-Benzyloxyphenylmercapto)quinazoline; 4-(4-Benzyloxyphenylmercapto)-6,7-dimethoxyquinazoline; 4-(4-Benzyloxybenzyloxy)quinazoline; 4-(4-Benzyloxybenzyloxy)-6,7-dimethoxyquinazoline; 6,7-Dimethoxy-4-(4-phenoxybenzylamino)quinazoline; 4-(Phenoxyanilino)quinazoline hydrochloride; 6,7-Dimethoxy-4-(4-phenoxyanilino)quinazoline hydrochloride; 4-(3-Benzyloxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6,7-dimethylquinazoline hydrochloride; 6,7-Dimethyl-4-(4-phenoxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-5-methoxyquinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6-methoxyquinazoline hydrochloride; 6-Acetoxy-4-(4-benzyloxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6-hydroxyquinazoline; 4-(4-Benzyloxyanilino)-7-methoxyquinazoline hydrochloride; 4-(4-Benzyloxyanilino)-7-hydroxyquinazoline; 7-Acetoxy-4-(4-benzyloxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-5,6-dimethoxyquinazoline hydrochloride; 5,6-Dimethoxy-4-(4-phenoxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6-fluoroquinazoline hydrochloride; 6-Fluoro-4-(4-phenoxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-7-fluoroquinazoline hydrochloride; 7-Fluoro-4-(4-phenoxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-7-chloroquinazoline hydrochloride; 4-(4-Benzyloxyanilino)-5-chloroquinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6-chloroquinazoline hydrochloride; 6-Chloro-4-(4-phenoxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6,7-dichloroquinazoline hydrochloride; 5-Chloro-4-(4-phenoxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6-bromoquinazoline hydrochloride; 6-Bromo-4-(4-phenoxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6-iodoquinazoline hydrochloride; 6-Iodo-4-(4-phenoxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6-trifluoromethoxyquinazoline hydrochloride; 4-(4-Benzyloxyanilino)-7-(trifluoromethyl)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6-nitroquinazoline hydrochloride; 6-Amino-4-(4-benzyloxyanilino)quinazoline; 4-(4-Benzyloxyanilino)-6-ureidoquinazoline; 6-Acetamido-4-(4-benzyloxyanilino)quinazoline; 6-Nitro-4-(4-phenoxyanilino)quinazoline hydrochloride; 6-Amino-4-(4-phenoxyanilino)quinazoline;

4-(4-Benzyloxyanilino)-7-nitroquinazoline hydrochloride; 7-Amino-4-(4-benzyloxyanilino)quinazoline; 4-(4-Benzyloxyanilino)-7-(3,3-dimethylureido)quinazoline; 4-(4-Benzyloxyanilino)-7-ureidoquinazoline; 7-Acetamido-4-(4-benzyloxyanilino)quinazoline; 7-Nitro-4-(4-phenoxyanilino)quinazoline; 7-Amino-4-(4-phenoxyanilino)quinazoline; 4-(4-Benzyloxyanilino)-6-methylthioquinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6-methylsulphonylquinazoline; 4-(4-Benzyloxyanilino)-6-methylsulphinylquinazoline; 6-Methylthio-4-(4-phenoxyanilino)quinazoline hydrochloride; 6,7-Diacetoxy-4-(4-benzyloxyanilino)quinazoline; 4-(4-Benzylaminoanilino)quinazoline hydrochloride; 4-(4-Benzylaminoanilino)-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Benzylanilino)quinazoline hydrochloride; 4-(4-Benzylanilino)-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Anilinoanilino)quinazoline hydrochloride; 4-(4-Anilinoanilino)-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Benzoylanilino)quinazoline hydrochloride; 4-(4-Benzoylanilino)-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Benzoylaminoanilino)quinazoline hydrochloride; 4-(4-Benzoylaminoanilino)-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Anilinocarbonylanilino)quinazoline hydrochloride; 4-(4-Anilinocarbonylanilino)-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Anilinomethylanilino)quinazoline hydrochloride; 4-(4-Phenylethynylanilino)quinazoline hydrochloride; 6,7-Dimethoxy-4-(4-phenylethynylanilino)quinazoline hydrochloride; (trans)-4-(4-Phenylethenyl)anilinoquinazoline hydrochloride; (trans)-6,7-Dimethoxy-4-(4-phenylethenylanilino)quinazoline hydrochloride; 4-(4-henylethylanilino)quinazoline hydrochloride; 6,7-Dimethoxy-4-(4-phenylethylanilino)quinazoline hydrochloride; 4-(4-Phenylthioanilino)quinazoline hydrochloride; 4-(4-phenylsulfonylanilino) quinazoline; 4-(4-phenylsulfinylanilino)quinazoline; 6,7-Dimethoxy-4-(4-phenylthioanilino)quinazoline hydrochloride; 6,7-Dimethoxy-4-(4-phenyl-sulfonylanilino)quinazoline; 6,7-dimethoxy-4-(4-phenylsulfinylanilino)quinazoline; 4-[4-(Benzylthio)anilino]quinazoline hydrochloride; 4-[4-(Benzylthio)anilino]-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Benzylsulfonylanilino)-6,7-dimethoxy-quinazoline; 4-(4-Phenylthiomethylanilino)quinazoline hydrochloride; 6,7-Dimethoxy-4-(4-phenylthiomethylanilino)quinazoline hydrochloride; 6,7-Dimethoxy-4-[4-(phenylsulfonylmethyl)anilino]quinazoline; 4-(4-Phenoxymethylanilino)quinazoline; 6,7-Dimethoxy-4-(4-phenoxymethyl-anilino)quinazoline; 4-[4-(2-Thienylmethoxy)anilino]quinazoline hydrochloride; 6,7-Dimethoxy-4-[4-(2-thienylmethoxy)anilino]quinazoline hydrochloride;

4-[4-(3-Thienylmethoxy)anilino]quinazoline hydrochloride; 6,7-Dimethoxy-4-[4-(3-thienylmethoxy)anilino]quinazoline hydrochloride; 4-[4-(Furan-2-methoxy)anilino]-quinazoline hydrochloride; 6,7-Dimethoxy-4-[4-(furan-2-methoxy)anilino]quinazoline hydrochloride; 4-[4-(Furan-3-methoxy)anilino]quinazoline hydrochloride; 6,7-Dimethoxy-4-[4-(furan-3-methoxy)anilino]quinozoline hydrochloride; (S)-4-{4-[(2-Oxo-4-oxazolinyl)methyl]anilino}quinazoline hydrochloride; (S)-6,7-Dimethoxy-4-{4-[(2-oxo-4-oxazolinyl)methyl]anilino}quinazoline hydrochloride; (R/S)-4-{4-[(3-Methyl-2-oxo-4-oxazolidinyl)methyl]-anilino]quinazoline hydrochloride; (R/S)-6,7-Dimethoxy-4-{4-[(3-methyl-2-oxo-4-oxazolidinyl) methyl]anilino]quinazoline hydrochloride; 4-[4-(2-thiazolyl)amino-sulphonyl] anilinoquinazoline hydrochloride; 6,7-Dimethoxy-4-[4-(2-thiazolyl)aminosulphonyl] anilinoquinazoline hydrochloride; 4-[4-(1,2,3-Thiadiazol-4-yl)anilino]quinazoline hydrochloride; 6,7-Dimethoxy-4-[4-(1,2,3-thiadiazol-4-yl)anilino]quinazoline hydrochloride; 4-(4-Cyclohexyl)anilino-quinazoline hydrochloride; 4-(4-Cyclohexyl)anilino-6,7-dimethoxyquinazoline hydrochloride; 4-[4-(Cyclohexylmethoxy)- anilino]quinazoline hydrochloride; 4-[4-(Cyclohexylmethoxy)-anilino]-6,7-dimethoxyquinazoline hydrochloride; 4-(4-methylmercapto-anilino)quinazoline hydrochloride; 4-(4-Methoxphenylthio)quinazoline; 6,7-Dimethoxy-4-(3-methylmercaptoanilino)quinazoline hydrochloride; 6,7-Dimethoxy-4-(3-phenoxyanilino)quinazoline hydrochloride; 6,7-Diethoxy-4-(3-phenoxy)anilinoquinazoline hydrochloride; 6,7-Diethoxy-4-(4-phenoxy)anilinoquinazoline hydrochloride; 4-(4-Benzyloxy)anilino-6,7-diethoxyquinazoline hydrochloride; 6,7-Methylenedioxy-4-(3-phenoxyanilino)quinazoline hydrochloride; 6,7-Methylenedioxy-4-(4-phenoxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6,7-methylenedioxyquinazoline hydrochloride; 6,7-Dimethoxy-2-methyl-4-(3-phenoxyanilino)quinazoline hydrochloride; 6,7-Dimethoxy-2-methyl-4-(4-phenoxyanilino)quinazoline hydrochloride; 4-(4-Benzyloxyanilino)-6,7-dimethoxy-2-methylquinazoline hydrochloride; 4-(4-Benzylanilino)-6,7-diethoxyquinazoline hydrochloride; 4-(4-Benzylanilino)-6,7-methylenedioxyquinazoline hydrochloride; 4-(4-Benzylanilino)-6-bromoquinazoline hydrochloride; 4-(4-Benzylanilino)-6,7-dimethoxy-2-methylquinazoline hydrochloride; 4-(4-Benzyloxy-2-methylanilino)quinazoline; 4-(4-Benzyloxy-2-methylanilino)-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Benzyloxy-3-chloroanilino)quinazoline hydrochloride; 4-(4-Benzyloxy-3-chloroanilino)-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Benzyloxy-3-chloroanilino)-6-bromoquinazoline hydrochloride;

4-(4-Benzyloxy-3-methoxyanilino)-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Benzyloxy-2-nitroanilino)quinazoline hydrochloride; 4-(4-Benzyloxy-2-nitroanilino)-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Benzyloxy-3,5-dibromoanilino)quinazoline hydrochloride; 4-(4-Benzyloxy-3,5-dibromoanilino)-6,7-dimethoxyquinazoline; 6-Bromo-4-(4-benzyloxy-3,5-dibromoanilino) quinazoline; 4-(4-Benzyloxy-2-trifluoromethylanilino)quinazoline; 4-(4-Benzyloxy-2-trifluoromethylanilino)-6,7-dimethoxyquinazoline; 4-(4-Benzyloxy-3-methylanilino)-6,7-dimethoxyquinazoline hydrochloride; 6-Bromo-4-(4-benzyloxy-3-methylanilino)quinazoline hydrochloride; 4-(4-Benzyloxy-3-fluoroanilino)quinazoline hydrochloride; 4-(4-Benzyloxy-3-fluoroanilino)-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Benzyloxy-3-fluoroanilino)-6-bromoquinazoline hydrochloride; 4-(4-Benzyloxy-3-trifluoromethylanilino)quinazoline hydrochloride; 4-(4-Benzyloxy-3-trifluoromethylanilino)-6,7-dimethoxyquinazoline hydrochloride; 4-(4-Benzyloxy-3-trifluoromethylanilino)-6-bromoquinazoline hydrochloride; 4-(4-Benzyloxy-3-cyanoanilino)quinazoline hydrochloride; 4-(4-Benzyloxy-3-cyanoanilino)-6,7-dimethoxyquinazoline dihydrochloride; 4-[4-(4-Chlorophenoxy)anilino]quinazoline hydrochloride; 4-[4-(4-Chlorophenoxy)anilino]-6,7-dimethoxyquinazoline hydrochloride; 4-[4-(2,4-Dichlorophenoxy)anilino]quinazoline hydrochloride; 4-[4-(2,4-Dichlorophenoxy)anilino]-6,7-dimethoxyquinazoline hydrochloride. 6-Bromo-4-[4-(2,4-dichlorophenoxy)anilino]quinazoline hydrochloride; 4-[3-(2-Methyl-4-pyrimidinyl)anilino]quinazoline hydrochloride; 4-[4-(1,3-Dioxolan-2-yl)methoxy]quinazoline hydrochloride; 4-[4-(1,3-Dioxolan-2-yl)methoxy]-6,7-dimethoxyquinazoline hydrochloride; 6-Bromo-4-[4-(1,3-dioxolan-2-yl)methoxy]quinazoline hydrochloride; 4-[4-(1-Morpholinyl)anilino]quinazoline hydrochloride; 4-[4-(1-Piperidinyl)anilino]quinazoline hydrochloride; 4-[4-(1,3-Dioxan-2-ylethoxy)anilino]quinazoline hydrochloride; 6,7-Dimethoxy-4-[4-(1,3-dioxan-2-ylethoxy)anilino]quinazoline hydrochloride; 6-Bromo-4'-[4-(1,3-dioxan-2-ylethoxy) anilino]quinazoline hydrochloride; 4-[4-(2-Bromobenzyloxy)-3-chloroanilino]quinazoline hydrochloride; 4-[4-(2-Bromobenzyloxy)-3-chloroanilino]-6,7-dimethoxyquinazoline hydrochloride; 4-[4-(2-Bromobenzyloxy)-3-chloro]anilino-6,7-diethoxyquinazoline hydrochloride; 6-Bromo-4-[4-(2-bromobenzyloxy)-3-chloroanilino]quinazoline hydrochloride; 4-[4-(2-Fluorobenzyloxy)-2-methylanilino]quinazoline hydrochloride; 6,7-Dimethoxy-4-[4-(2-fluorobenzyloxy)-2-methyl]anilinoquinazoline hydrochloride; 6-Bromo-4-[4-(2-fluorobenzyloxy)-2-methyl]anilinoquinazoline hydrochloride; 4-[4-(2-Bromobenzyloxy)-3-methoxyanilino]quinazoline hydrochloride; 4-[4-(2-Bromobenzyloxy)-3-methoxyanilino]-6,7-dimethoxyquinazoline; hydrochloride;

4-[4-(2-Bromobenzyloxy)-3-methoxy]anilino-6,7-diethoxyquinazoline hydrochloride; 6-Bromo-4-[4-(2-bromobenzyloxy)-3-methoxyanilino]quinazoline hydrochloride; 4-[3-Chloro-4-(2,4-dichlorophenoxy)anilino]quinazoline hydrochloride; 4-[3-Chloro-4-(2,4-dichlorophenoxy)anilino]-6,7-dimethoxyquinazoline; hydrochloride; 6-Bromo-4-[3-chloro-4-(2,4-dichlorophenoxy)anilino]quinazoline hydrochloride; 4-[3-Chloro-4-(2-fluorobenzyloxy)anilino]quinazoline hydrochloride; 4-[3-Chloro-4-(2-fluorobenzyloxy)anilino]-6,7-dimethoxyquinazoline hydrochloride; 4-[3-Chloro-4-(2-fluorobenzyloxy)]anilino-6,7-diethoxyquinazoline hydrochloride; 6-Bromo-4-[3-chloro-4-(2-fluorobenzyloxy)anilino]quinazoline hydrochloride; 4-[4-(2,6-Dichlorobenzyloxy)-3-methoxyanilino]quinazoline hydrochloride; 4-[4-(2,6-Dichlorobenzyloxy)-3-methoxyanilino]-6,7-dimethoxyquinazoline; hydrochloride; 4-[4-(2,6-Dichlorobenzyloxy)-3-methoxyanilino]-6,7-diethoxyquinazoline hydrochloride; 6-Bromo-4-[4-(2,6-dichlorobenzyloxy)-3-methoxy]anilinoquinazoline hydrochloride; 4-[4-(2,6-Difluorobenzyloxy)-3-methoxyanilino]quinazoline hydrochloride; 4-[4-(2,6-Difluorobenzyloxy)-3-methoxyanilino]-6,7-dimethoxyquinazoline; hydrochloride; 6,7-Diethoxy-4-[4-(2,6-difluorobenzyloxy)-3-methoxyanilino]quinazoline hydrochloride; 6-Bromo-4-[4-(2,6-difluorobenzyloxy)-3-methoxyanilino]quinazoline hydrochloride; 4-[3-Methoxy-4-(2-methoxybenzyloxy)]anilinoquinazoline hydrochloride; 6,7-Dimethoxy-4-[3-methoxy-4-(2-methoxybenzyloxy)]anilinoquinazoline hydrochloride; 6,7-Diethoxy-4-[3-methoxy-4-(2-methoxybenzyloxy)]anilinoquinazoline hydrochloride; 6-Bromo-4-[3-methoxy-4-(2-methoxybenzyloxy)]anilinoquinazoline hydrochloride; 4-[3-Chloro-4-(2-methoxybenzyloxy)]anilinoquinazoline hydrochloride; 4-[3-Chloro-4-(2-methoxybenzyloxy)]anilino-6,7-dimethoxyquinazoline hydrochloride; 4-[3-Chloro-4-(2-methoxy benzyloxy)]anilino-6,7-diethoxyquinazoline hydrochloride; 4-[3-Chloro-4-(2-methoxybenzyloxy)anilino]-6,7-methylenedioxyquinazoline; hydrochloride; and 6-Bromo-4-[3-chloro-4-(2-methoxybenzyloxy)]anilinoquinazoline hydrochloride; and pharmaceutically acceptable salts thereof.

Preferred compounds of the present invention include:
4-(4-Phenoxyanilino)quinoline; 4-(4-Benzyloxyanilino)quinoline;
4-(4-Benzyloxyanilino)-6,7-dimethoxyquinoline; 5-Chloro-2-[4-(6,7-dimethoxy-4-quinolylamino)-2-methylphenyl]isoindol-1,3-dione;
4-(4-Benzyloxyphenoxy)quinazoline; 6,7-Dimethoxy-4-(4-phenoxyanilino)quinazoline; 4-(3-Benzyloxyanilino)quinazoline;
4-(4-Benzyloxyanilino)quinazoline; 4-(4-Benzyloxyanilino)-6,7-dimethoxyquinazoline; 4-(4-Benzyloxyanilino)-6,7-dimethylquinazoline;

4-(4-Benzyloxyanilino)-5-methoxyquinazoline; 4-(4-Benzyloxyanilino)-6-methoxyquinazoline; 4-(4-Benzyloxyanilino)-7-methoxyquinazoline; 4-(4-Benzyloxyanilino)-7-chloroquinazoline; 4-(4-Benzyloxyanilino)-6-bromoquinazoline; 6-Nitro-4-(4-phenoxyanilino)quinazoline; 4-(4-Anilinoanilino)-6,7-dimethoxyquinazoline; 4-(4-Benzyloxy-3-methoxyanilino)-6,7-dimethoxyquinazoline; 4-[4-(2-Thienylmethoxy)anilino]quinazoline; and pharmaceutically acceptable salts thereof.

Particularly preferred compounds of the present invention are: 4-(4-benzyloxyanilino)quinazoline and 4-(4-benzyloxyanilino)-6,7-dimethoxyquinazoline; and pharmaceutically acceptable salts thereof.

By halo is meant fluoro, chloro, bromo or iodo.

Alkyl groups containing three or more carbon atoms may be straight, branched or cyclised.

Heterocyclic groups comprise one or more rings which may be saturated, unsaturated, or aromatic and which may independently contain one or more heteroatoms in each ring.

Carbocyclic groups comprise one or more rings which may be independently saturated, unsaturated or aromatic and which contain only carbon and hydrogen.

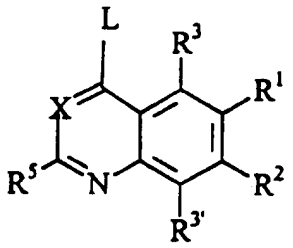
Optional substituents include, but are not limited to, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, nitro, amino, cyano, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkyl carbonyl, carboxylate, C_{1-4} alkoxy carbonyl, carboxamide, C_{1-4} alkylamino carbonyl and di[C_{1-4} alkyl]amino.

Certain compounds of the formula (I) contain asymmetric carbon atoms and are, therefore, capable of existing as optical isomers. The individual isomers and mixtures of these are included within the scope of the present invention. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula.

Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen in the compound of formula (I). The therapeutic activity resides in the moiety derived from the compound of the invention as defined herein and

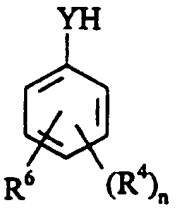
the identity of the other component is of less importance although for therapeutic and prophylactic purposes it is, preferably, pharmaceutically acceptable to the patient. Examples of pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acids, and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycollic, gluconic, succinic and methanesulphonic and arylsulphonic, for example p-toluenesulphonic, acids.

In a further aspect, the present invention provides a process for the preparation of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, which process comprises the reaction of a compound of the formula (II).



(II)

with a compound of the formula III :



(III)

wherein L is a leaving group and X, Y and R^1 to R^6 are as hereinbefore defined. Suitable leaving groups will be well known to those skilled in the art and include, for example, halo such as chloro and bromo; sulphonyloxy groups such as methanesulphonyloxy and toluene-p-sulphonyloxy; and alkoxy groups.

The reaction is conveniently carried out in the presence of a suitable inert solvent, for example a C_{1-4} alkanol, such as isopropanol, a halogenated hydrocarbon, an ether, an aromatic hydrocarbon or a dipolar aprotic solvent such as acetone at a non-extreme temperature, for example from 0 to 150°, suitably 10 to 100°C, preferably 50 to 100°C.

Optionally, the reaction is carried out in the presence of a base when Y = NH. Examples of suitable bases include an organic amine such as triethylamine, or an alkaline earth metal carbonate, hydride or hydroxide, such as sodium or potassium carbonate, hydride or hydroxide. When YH = OH or SH it is necessary to perform the reaction in the presence of a base, and in such a case the product is not obtained as the salt.

The compound of formula (I) in the case in which Y = NR^b may be obtained from this process in the form of a salt with the acid HL, wherein L is as hereinbefore defined, or as the free base by treating the salt with a base as hereinbefore defined.

The preparation of compounds (II) and (III) is well known to those skilled in the art.

In addition to the above, one compound of formula (I) may be converted to another compound of formula (I) by chemical transformation of the appropriate substituent or substituents using appropriate chemical methods (see for example, J.March "Advanced Organic Chemistry", Edition III, Wiley Interscience, 1985).

For example a compound containing an alkyl or aryl mercapto group may be oxidised to the corresponding sulphinyl or sulphonyl compound by use of an organic peroxide (eg benzoyl peroxide) or suitable inorganic oxidant (eg OXONE ®)

A compound containing a nitro substituent may be reduced to the corresponding amino-compound, eg by use of hydrogen and an appropriate catalyst (if there are no other susceptible groups) or by use of Raney Nickel and hydrazine hydrate.

Amino or hydroxy substituents may be acylated by use of an acid chloride or an anhydride under appropriate conditions. Equally an acetate or amide group may be cleaved to the hydroxy or amino compound respectively by treatment with, for example, dilute aqueous base.

In addition reaction of an amino substituent with triphosgene and another amine (eg aqueous ammonia, dimethylamine) gives the urea substituted product.

An amino substituent may also be converted to a dimethylamino substituent by reaction with formic acid and sodium cyanoborohydride.

The present invention also provides compounds of formula (I) and pharmaceutically acceptable salts thereof (hereinafter identified as the 'active compounds') for use in medical therapy, and particularly in the treatment of disorders mediated by aberrant protein tyrosine kinase activity such as human malignancies and the other disorders mentioned above. The compounds are especially useful for the treatment of disorders caused by aberrant c-erbB-2 activity such as breast, ovarian, non-small cell lung, pancreatic, gastric and colon cancers.

A further aspect of the invention provides a method of treatment of the human or animal body suffering from a disorder mediated by aberrant protein tyrosine kinase activity which comprises administering an effective amount of a compound of formula (I),or a pharmaceutically acceptable salt thereof, to the human or animal patient.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of malignant tumours.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of atherosclerosis, resterosis or thrombosis.

A further aspect of the present invention provides a pharmaceutical formulation comprising one or more compounds of formula (I), or pharmaceutically acceptable salt(s) thereof, together with one or more pharmaceutically carriers.

Whilst it is possible for the compounds or salts of the present invention to be administered as the new chemical, it is preferred to present them in the form of a pharmaceutical formulation.

According to a further feature of the present invention we provide pharmaceutical formulations comprising at least one compound of the formula (I) together with one or more pharmaceutically acceptable carriers or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain for example 0.5mg to 1g, preferably 5mg to 100mg of a compound of the formula (I) depending on the condition being treated, the route of administration and the age, weight and condition of the patient.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the

type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds and salts of the formula (I) have anticancer activity as demonstrated hereinafter by their inhibition of the protein tyrosine kinase c-erbB-2 enzyme. It has thus been established that compounds of the present invention are of use in medicine and, in particular in the treatment of certain human malignancies, for example breast, ovarian non-small cell lung, pancreatic, gastric and colon cancers. Accordingly, the present invention provides a method for the treatment of susceptible malignancies in an animal, e.g. a human, which comprises administering to the animal a therapeutically effective amount of a compound or salt of the present invention. In the alternative, there is also provided a compound or salt of the present invention for use in medicine and, in particular, for use in the treatment of cancers.

The present invention also provides the use of a compound of formula (I) or a salt thereof for the manufacture of a medicament for treatment of malignant tumours.

The animal requiring treatment with a compound or salt of the present invention is usually a mammal, such as a human being.

A therapeutically effective amount of a compound or salt of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. However, an effective amount of a compound of the present invention for the treatment of neoplastic growth, for example colon or breast carcinoma will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt of the present invention may be determined as a proportion of the effective amount of the compound per se.

General Experimental Details

Certain embodiments of the present invention will now be illusttrated by way of example only. The physical data given for the compounds exemplified is consistent with the assigned structure of those compounds.

IR spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer or a Bruker FS66 spectrophotometer.

1H NMR spectra were obtained on a Bruker WM 360-NMR spectrophotometer at 360MHz, or on a Bruker AC200 spectrophotometer at 200 MHz. J values are given in Hz.

Mass spectra were obtained on Varian CH5D (EI), Kratos Concept (EI) or Kratos Ms50 (FAB) machines.

Analytical thin layer chromatography (tlc) was used to verify the purity of some intermediates which could not be isolated or which were too unstable for full characterisation, and to follow the progess of reactions. Unless otherwise stated, this was done using silica gel (Merck Silica Gel 60 F254).

Unless otherwise stated, column chromatography for the purification of some compounds, used Merck Silica gel 60 (Art. 1.09385, 230-400 mesh), and the stated solvent system under pressure.

Petrol refers to petroleum ether, either the fraction boiling at 40-60°C, or at 60-80°C.

Ether refers to diethylether.

THF refers to tetrahydrofuran.

DMF refers to dimethylformamide.

DCM refers to dichloromethane.

DMSO refers to dimethylsulphoxide

Hydrogen peroxide refers to the commercially available aqueous solution with a concentration of 30-35% by weight.

The term '4-hydoxyqinazoline' and 'quinazolin-4-(1H)-one' are different tautomeric representations of the same structure.

General Synthetic Procedures

Procedure A - First method for reaction of an amine and a 4-chloroquinazoline or quinoline:

The 4-chloroquinazoline or 4-chloroquinoline (optionally substituted) was suspended in 2-propanol and heated to *ca* 80°C. The amine was added and the mixture was heated at reflux until judged complete (for example, by no 4-chloro starting material remaining by tlc), and then allowed to cool. The resulting

suspension may be diluted, *e.g.* with acetone, and the solid was collected by filtration, washed, and dried at 60°C *in vacuo*.

Procedure B - Second method for the same reaction:

The 4-chloroquinazoline or 4-chloroquinoline (optionally substituted) and an amine were mixed in 2-propanol and heated to reflux. When the reaction was complete, the mixture was allowed to cool. The resulting suspension was diluted, *e.g.* with acetone, and the solid collected by filtration, washed, and dried at 60°C *in vacuo*.

Procedure C - Third method for the same reaction:

The 4-chloroquinazoline (optionally substituted) and an amine were mixed in 2-propanol and heated under reflux. When the reaction was complete the mixture was allowed to cool. The resultant solid was collected by filtration, washing with isopropanol, isopropanol:ether (1:1) and finally with ether. A suspension of the resultant hydrochloride salt in dichloromethane was basified with triethylamine, and the resultant solution evaporated to dryness. The free base was purified by chromatography on silica gel using methanol/dichloromethane mixtures as mobile phase.

Procedure D - Conversion of a 4-hydroxyquinazoline to a 4-chloroquinazoline using phosphorous oxychloride:

The 4-hydroxyquinazoline, phosphorus oxychloride and triethylamine were reacted at reflux under nitrogen. The excess reagents were removed at 70°C under vacuum and the residue extracted several times with quantities of boiling 60-80 Petrol. The combined extracts were concentrated under vacuum.

Procedure E - first method for the preparation of a substituted 4-benzyloxynitrobenzene:

An appropriately substituted 4-nitrophenol (15.0 mmol) was added portionwise to a stirred suspension of sodium hydride (0.40 g; 16.5 mmol) in dry dimethylformamide (40 ml) at room temperature under nitrogen. Stirring was continued until evolution of hydrogen had ceased. An appropriately substituted benzyl halide (16.0 mmol) was then added in one portion and the mixture stirred at 40-90°C until judged complete by thin layer chromatography. After cooling to 30°C, the mixture was poured into stirred ice/water (100 g) and the precipitated solid collected by filtration, washed with water and dried *in vacuo* to give the corresponding 4-benzyloxynitrobenzene. The product was used (unless stated otherwise) without further purification.

Procedure F - second method for the same reaction:

As for Procedure E but potassium iodide (1.0 g) was added to the mixture immediately following the appropriately substituted benzyl halide.

Procedure G - third method for the same reaction:

An appropriately substituted 4-nitrophenol (1.0 mmol), an appropriately substituted benzyl alcohol (1.2 mmol) and dicyclohexylcarbodiimide (0.227 g; 1.1 mmol) were

heated together at 100-110°C until the reaction was judged complete by tlc. After cooling to 20°C, the mixture was dissolved in dichloromethane (30 ml) and the resulting solution extracted with 1M aqueous sodium hydroxide (3 x 10 ml), dried (Na_2SO_4), filtered through a pad of Hyflo and silica gel and evaporated to dryness. Purification was affected by flash chromatography on silica gel using dichloromethane-hexane mixtures as eluent.

General Procedure H - reduction of a substituted nitrobenzene to a substituted aniline:
To a stirred mixture of washed (3 x 15 ml methanol) Raney nickel (Fluka) (0.50 g) and the appropriately substituted nitrobenzene (5 mmol) in methanol (25 ml) under nitrogen was added dropwise hydrazine hydrate (0.75 g; 15 mmol) keeping the temperature below 40°C. When the addition was complete and brisk evolution of nitrogen had ceased, the mixture was stirred at 50°C for 20 minutes, cooled to 20°C, filtered through a pad of Hyflo and evaporated under reduced pressure to give the corresponding substituted aniline. The product was used without further purification.

4-Chloroquinoline is commercially available.

4-Chloro-6,7-dimethoxyquinoline was prepared by by the reaction of 6,7-dimethoxy-4-hydroxyquinoline (5.7g, 27.78 mmol) with phosphorous oxychloride (7.6 ml, 81.54 mmol) in toluene (45 ml) at reflux for 2 hours. The mixture was concentrated in vacuo at 50°C to give a solid, which was washed with sat. aq. potassium carbonate solution (200 ml) and water, and dried at 60°C in vacuo to give the compound as an off-white solid (6.29g, quant.); δH [$^2H_6$]-DMSO 8.84 (1H, d, J 5.5, 2-H), 7.79 (1H, d, J 5.5, 3-H), 7.67 (1H, s, 8-H), 7.56 (1H, s, 5-H), 4.14 (6H, s, 2 x CH_3).

4-Chloro-2-methylquinoline (also known as 4-chloroquinaldine) is commercially available.

4-Chloroquinazoline was prepared from 4-hydroxyquinazoline (commercially available) according to the published method (J. Org. Chem, 27, 958 (1962)).

4-Chloro-6,7-dimethylquinazoline was prepared from 3,4-dimethyl-6-nitroaniline as follows:
4,5-Dimethyl-2-nitroaniline (commercially available) (25.0g, 150.4 mmol) was added to conc HCl (35 ml) and heated to reflux. The solution was cooled to 0°C and an aqueous solution of sodium nitrite (10.42g, 151 mmol in 37 ml) was added

dropwise. After addition was complete, the slurry was stirred for 45 minutes at 0°C and then added over 30 min to a mixture of potassium cyanide (41.66g, 640 mmol) and copper sulphate (37.94g, 152 mmol) dissolved in water (190 ml) at reflux. The resulting mixture was filtered while hot, and the solid thus obtained treated with a large excess of ethyl acetate. The solution was dried and concentrated in vacuo to a red solid, which was washed with ethyl acetate/petrol (1:1) to leave an orange solid. Chromatography, eluting with ethyl acetate/cyclohexane (gradient elution, 0% - 40%) gave 4,5-dimethyl-2-nitrobenzonitrile as an orange solid (9.176g, 35%); δH [$^2H_6$]-DMSO 8.19 and 7.95 (2 x 1H, 2 x s, 3-H, 6-H), 2.41 and 2.39 (2 x 3H, 2 x s, 2 x CH_3).

4,5-Dimethyl-2-nitrobenzonitrile (7.225g, 40.5 mmol) was dissolved in DMSO (35 ml) and cooled to 0°C. Potassium carbonate (0.85g, 6.15 mmol) was added, followed by hydrogen peroxide solution (5.1 ml), giving an exothermic reaction and forming a dark brown solid. The mixture was stirred at room temp. for 30 min, diluted with water to a total volume of 250 ml and filtered. The precipitate was washed with water and dried in vacuo at 60°C to give 4,5-dimethyl-2-nitrobenzamide (7.0g, 89%); δH [$^2H_6$]-DMSO 7.93 and 7.50 (2 x 1H, 2 x br s, 2 x NH), 7.80 and 7.41 (2 x 1H, 2 x s, 3-H, 6-H), 2.39 (6H, s, 2 x CH_3).

4,5-Dimethyl-2-nitrobenzamide (7.0g, 36.0 mmol) was added to an aqueous solution of iron (II) sulphate heptahydrate (100g in 150 ml), and the suspension heated to reflux. Saturated aq. ammonia solution (50 ml) was added slowly, causing the mixture to turn black, and it was heated at reflux for 15 min and allowed to cool. The mixture was filtered, and the solid was treated with boiling ethanol to give an orange solution, which was concentrated to an orange solid. This was dissolved in ethyl acetate, filtered and concentrated to a solid. Trituration with ethyl acetate/petrol (1:1) gave a first batch of pale orange crystals. The ethyl acetate/petrol solution from the trituration was concentrated and triturated again to give a second batch of orange crystals. These two batches were combined and dried at 60°C to give 2-amino-4,5-dimethylbenzamide (4.68g, 79%); δH [$^2H_6$]-DMSO 7.30 (1H, s, 3-H) and 6.49 (1H, s, 6-H), 6.19 (2H, br s, NH_2), 2.10 and 2.08 (2 x 3H, 2 x s, 2 x CH_3).

2-Amino-4,5-dimethylbenzamide (4.0g, 2.44 mmol) and formic acid (15 ml) were mixed and heated at 130°C for 4 hours, giving a pale orange solution. This was allowed to cool to room temperature and diluted with acetone, giving cream crystals, which were collected by filtration, washing with acetone. The filtrate was concentrated in vacuo to a yellow solid, which was triturated with acetone to give a second batch of product as a cream solid. The combined batches gave 6,7-dimethyl-

4-hydroxyquinazoline (3.58g, 84%) with mp 254-255oC ; (Found: C, 68.63; H, 5.77 N, 15.71. $C_{10}H_{10}N_2O$ requires: C, 68.95; H, 5.79; N, 16.08%); δH [$^2H_6$]-DMSO 11.96 (1H, br s, O-H), 7.99 (1H, s, 2-H), 7.89 (1H, s, 8-H), 7.49(1H, s, 5-H), 2.41 and 2.40 (2 x 3H, 2 x s, 2 x CH_3); m/z (%) 174 (100, M^+), 159 (58); ν_{max} (KBr disc)/cm^{-1} 1684, 1662, 1618.

6,7-Dimethyl-4-hydroxyquinazoline (0.62g, 3.56 mmol), phosphorous oxychloride (2.6 ml, 27.9 mmol) and triethylamine (1.1 ml, 7.89 mmol) were combined and heated to reflux under nitrogen for 3 hours. After standing at room temperature overnight, the mixture was concentrated in vacuo, and the resulting brown residue was treated with ethyl acetate. The mixture was filtered, and concentrated to a sticky brown solid. This was treated with petrol, and the petrol solution was filtered and concentrated to a white crystalline solid, which was dried in vacuo at 60°C to give 4-chloro-6,7-dimethylquinazoline (0.440g, 64%); δH [$^2H_6$]-DMSO 8.74 (1H, s, 2-H), 7.94 (1H, s, 8-H), 7.61(1H, s, 5-H), 2.39 and 2.38 (2 x 3H, 2 x s, 2 x CH_3).

4-Chloro-6,7-dimethoxyquinazoline was prepared according to the procedure described in European Patent Application 566 226 A1 (Zeneca Limited). This synthetic route includes the preparation of 4-hydroxy-6,7-dimethoxyquinazoline.

4-Chloro-6-methoxyquinazoline was prepared according to the procedure described in European Patent Application 566 226 A1 (Zeneca Limited).

4-Chloro-7-methoxyquinazoline was prepared according to the procedure described in European Patent Application 566 226 A1 (Zeneca Limited).

4,7-Dichloroquinazoline was prepared according to the procedure described in European Patent Application 566 226 A1 (Zeneca Limited).

6-Acetoxy-4-chloroquinazoline was prepared according to the procedure described in European Patent Application 566 226 A1 (Zeneca Limited).

7-Acetoxy-4-chloroquinazoline was prepared from 4,7-dihydroxyquinazoline as follows:

Acetic anhydride (9ml, 88mmol) was added dropwise over 10 minutes to a stirred mixture of 4,7-dihydroxyquinazoline (prepared as described in Chim. Ther., 2, (4), 231-9, 1967) (0.900g, 5.6mmol) and triethylamine (9ml, 68mmol) in DMF (30ml). The reaction was stirred at ambient temperature for 3 hours, and the solvent removed under

vacuum. The resulting oil was triturated with toluene to give 7-acetoxy-4-hydroxyquinazoline as a brown solid (1.10g, 99%); δH [$^2H_6$] -DMSO 8.15 (1H, s, 2-H), 8.10 (1H, d, 5-H), 7.40 (1H, s, 8-H), 7.29 (1H, d, 6-H), 2.31 (3H, s, CH_3).
7-Acetoxy-4-hydroxyquinazoline (1.1g, 5.4mmol), triethylamine (3.0ml, 23mmol) and phosphorus oxychloride (4.0ml, 43mmol) were reacted at reflux for 2 hours. Once cold the resulting oil was extracted with boiling heptane containing 5% triethylamine. The combined extracts were washed with aqueous ammonium hydroxide solution, dried ($MgSO_4$) and concentrated under vacuum to give 7-acetoxy-4-chloroquinazoline as a yellow solid (0.50g, 42%); δH [$^2H_6$] -DMSO 8.20 (1H, s, 2-H), 8.16 (1H, d, 5-H), 7.44 (1H, s, 8-H), 7.31 (1H, d, 6-H), 2.31 (3H, s, CH_3).

4-Chloro-5-methoxyquinazoline was prepared from 1,3-dinitrobenzene as follows:
1,3-Dinitrobenzene (commercially available) (25.0g, 148.7 mmol) was dissolved in methanol (375ml) and heated to 40°C. An aqueous solution of potassium cyanide (11.5g, 176.6 mmol in 20 ml) was added giving a dark solution, which was stirred at 40°C for 2 hours and then left to stand at room temperature for 2 days. The dark red mixture was filtered to yield a black solid. The filtrate was diluted with water (3000ml), left to stand overnight and filtered to yield further solid. The solids were combined and extracted with chloroform in a soxhlet apparatus for 1.5 hours. The extract was concentrated to a red solid. Chromatography on silica, eluting with toluene gave 6 methoxy-2-nitrobenzonitrile as a yellow solid (3.6g, 14%); δH [$^2H_6$]-DMSO 7.89-7.94 (2H, m, 3-H, 5-H), 7.72-7.78 (1H, m, 4-H), 4.03 (3H, s, OCH_3).
6-Methoxy-2-nitrobenzonitrile (3.6g, 20.2 mmol) was dissolved in DMSO (25 ml) and cooled to 0°C. Potassium carbonate (0.425g, 3.08 mmol) was added, followed by hydrogen peroxide solution (2.6 ml). The reaction was stirred at room temperature for 1 hour and further hydrogen peroxide (3 x 2.6 ml) added over the following hour to give an orange solution. The mixture was poured into water (200 ml), giving a white solid. This was collected by filtration, washed with water and dried in vacuo at 60°C to give 6-methoxy-2-nitrobenzamide (2.3g, 58%); δH [$^2H_6$]-DMSO 7.44-7.88 (5 H, m, 3-H, 4-H, 5-H, $CONH_2$), 3.83 (3H, s, OCH_3).
6-Methoxy-2-nitrobenzamide (2.2g, 11.2 mmol) was added to an aqueous solution of iron (II) sulphate heptahydrate (31.5g in 50 ml), and the suspension heated to reflux. Saturated aq. ammonia solution (16 ml) was added slowly, causing the mixture to turn black, and it was heated at reflux for 10 min and allowed to cool. The mixture was filtered, and the solid was treated with boiling ethanol to give a solution, which was concentrated to a white solid. This was dissolved in ethyl

acetate, filtered and concentrated to a solid to give 2-amino-6-methoxybenzamide (1.27g, 68%); δH [$^2H_6$]-DMSO 7.49 and 7.13 (2 x 1H, 2 x br s, $CONH_2$), 7.00 (1H, t, J 9, 4-H), 6.28-6.38 (3H, m, 5-H, NH_2), 6.19 (1H, d, J 9, 3-H), 3.78 (3H, s, OCH_3).

2-Amino-6-methoxybenzamide (1.2g, 7.22 mmol) and formic acid (10 ml) were mixed and heated to reflux for 5 hours. The excess formic acid was removed in vacuo to give a yellow oil, which crystallised on scratching. The crystals were triturated with acetone to give 5-methoxy-4(1H)quinazolinone as white crystals (0.720g, 53%) ; δH [$^2H_6$]-DMSO 8.15 (1H, s, N-H), 7.93 (1H, s, 8-H), 7.69 (1H, t, J 8, 7-H), 7.18 (1H, d, J 9, 8-H), 6.99(1H, d, J 9, 6-H), 3.88(3H, s, OCH_3).

5-Methoxy-4(1H)quinazolinone (0.68g, 3.86 mmol), phosphorous oxychloride (2.6 ml, 27.9 mmol) and triethylamine (1.1 ml, 7.89 mmol) were combined and heated to reflux under nitrogen for 1 hour. The mixture was concentrated in vacuo, and the resulting brown residue was extracted with hot heptane (x4). The petrol solution was concentrated to a yellow solid, which was dried in vacuo at 60°C to give 4-chloro-5-methoxyquinazoline (0.210g, 28%), which was used (see below) without further characterisation.

4-Chloro-5,6-dimethoxyquinazoline was prepared from 5,6-dimethoxy-2-nitrobenzonirile as follows:

To 5,6-dimethoxy-2-nitrobenzonitrile (2.2g, 10.6mmol, J. Med. Chem., 30, 1421-1426, 1987) in DMSO (20ml) at 0°C was added potassium carbonate (0.3g, 2.2mmol) and hydrogen peroxide (5ml, 30%). The reaction was stirred at ambient temperature for 15 minutes and the DMSO removed under vacuum. The residue was dissolved in ethyl acetate, filtered and the filtrate concentrated under vacuum. Trituration with ethyl acetate/ether gave 5,6-dimethoxy-2-nitrobenzamide as an orange solid (1.22g, 51%); δH [$^2H_6$] -DMSO 7.98 (1H, d), 7.78 (1H, b, CONH), 7.50 (1H, b, CONH), 7.25 (1H, d), 3.94 (3H, s), 3.77 (3H, s).

5,6-Dimethoxy-2-nitrobenzamide (1.2g, 5.3mmol) was added to a boiling solution of ferrous sulphate heptahydrate (15g) in water (25ml) and the solution heated to reflux. .880 ammonia (15ml) was then added and the mixture kept at reflux for 5 minutes, and then allowed to cool. The cold reaction was filtered and the residue extracted with hot ethanol. The ethanol extracts were concentrated under vacuum, dissolved in ethyl acetate and filtered. The filtrate was concentrated under vacuum to give 5,6-dimethoxyanthranilamide as a brown oil which crystallised upon standing. (1.0g, 96%).

5,6-Dimethoxyanthranilamide (1.2g, 6.1mmol) and formic acid (10ml) were reacted at reflux for 5 hours. The excess formic acid was removed under vacuum and the residual oil purified on a silica gel flash column eluting with a methanol/chloroform gradient (0-4% methanol) to give 5,6-dimethoxy-4-hydroxyquinazoline as an off-white solid (600mg, 48%); δH [$^2H_6$] -DMSO 11.79 (1H, br, OH), 7.85 (1h, s, 2-H), 7.58 (1H, d), 7.40 (1H, d), 3.86 (3H, s), 3.76 (3H, s).

5,6-Dimethoxy-4-hydroxyquinazoline (550mg, 2.7mmol), phosphorus oxychloride (2ml, 21.5mmol) and triethylamine (1ml, 7.2mmol) were reacted for 30 minutes according to Procedure D to give 4-chloro-5,6-dimethoxyquinazoline as a yellow crystalline solid (400mg, 67%), which was used further (see below) without characterisation due to instability.

4-Chloro-6-fluoroquinazoline was prepared from 4-fluoroanthranilic acid as follows:

5-Fluoroanthranilic acid (Aldrich) (1.0g, 6.4mmol) and formamidine acetate (2g, 19mmol) were reacted in glacial acetic acid (10ml) at reflux for 1.5 hours. The reaction was concentrated under vacuum and water added, forming a precipitate. This was collected by filtration and dried at 60°c under vacuum to give 6-fluoro-4-hydroxyquinazoline as an off-white solid (0.770g, 73%). δH [$^2H_6$] -DMSO 12.20 (1H, br, OH), 8.09 (1H, s, 2-H), 7.83-7.62 (3H, m, 5-H, 7-H, 8-H).

6-Fluoro-4-hydroxyquinazoline (0.580g, 3.5mmol), phosphorus oxychloride (2.6ml, 28mmol) and triethylamine (1.4ml, 10mmol) were reacted for 2 hours according to Procedure D. The solid was re-extracted into boiling 60-80 petrol, filtered while hot and the filtrate concentrated under vacuum to give 4-chloro-6-fluoroquinazoline as a white solid (0.365g, 57%).

4-Chloro-7-fluoroquinazoline

7-Fluoro-4-hydroxyquinazoline (Eur. Pat. 94305195.3) (0.500g, 3.0mmol), phosphorus oxychloride (2.3ml, 25mmol) and triethylamine (1.2ml, 8.6mmol) were reacted for 2 hours according to Procedure D. The solid was re-extracted into boiling 60-80 petrol, filtered while hot and the filtrate concentrated under vacuum to give 4-chloro-7-fluoroquinazoline as a white solid (0.550g, 100%).

4,5-Dichloroquinazoline

5-Chloro-4-hydroxyquinazoline (prepared according to J. Org. Chem., 141-148, 1951) (0.640g, 3.5mmol), phosphorus oxychloride (2.6ml, 28mmol) and triethylamine (1.4ml, 10mmol) were reacted for 2 hours according to Procedure D to give 4,5-

dichloroquinazoline as a cream solid (0.500g, 71%), which was not further characterised.

4,6-Dichloroquinazoline

6-Chloro-4-hydroxyquinazoline (prepared according to J. Org. Chem., 141-148, 1951) (0.640g, 3.5mmol,), phosphorus oxychloride (2.6ml, 28mmol) and triethylamine (1.1ml, 7.9mmol) were reacted at reflux under nitrogen for 3.5 hours. The excess reagents were removed at 70°C under vacuum and the reaction extracted with ethyl acetate (250ml). Petrol (250ml) was added to the extract and the solution decanted from the brown oil which separated. The decanted solution was concentrated under vacuum to give 4,6-dichloroquinazoline as a white solid (0.540g, 77%); δH [$^2H_6$]-DMSO 8.43 (1H, s, 2-H), 8.07 (1H, s, 5-H), 7.39 (1H, d, 7-H), 7.78 (1H, d, 8-H).

4,6,7-Trichloroquinazoline

6,7-Dichloro-4-hydroxyquinazoline (prepared according to J. Org. Chem., 149-156, 1951) (0.140g, 0.65mmol), phosphorus oxychloride (0.5ml, 5.4mmol) and triethylamine (0.2ml, 1.4mmol) were reacted for 1.5 hours according to Procedure D to give 4,6,7-trichloroquinazoline as a yellow solid (0.070mg, 46%).

6-Bromo-4-chloroquinazoline

6-Bromo-4-hydroxyquinazoline (Maybridge Chemicals) (2.25 g; 10mmol) was added to a mixture of triethylamine (3 ml) and phosphoryl chloride (7 ml) at room temperature. After heating at reflux for 3 hours, the tan mixture was cooled to 50°C and evaporated to dryness under reduced pressure. The tan residue was dissolved in ethyl acetate (200 ml) and the solution washed with water (3 x 100 ml) and 5% aqueous potassium hydrogen carbonate solution (2 x 100 ml). After drying (Na_2SO_4), the ethyl acetate solution was treated with charcoal (1 g), filtered and evaporated to dryness. The pale tan solid (2.5 g) was dissolved in boiling toluene. After standing at 0°C, the solid deposited was collected by filtration, washed with hexane and dried to give the product as pale yellow needles (1.68 g, 69%) with mp 166-167°C; (Found C, 39.64; H, 1.62; N, 11.47. $C_8H_4BrClN_2$ requires C, 39.42; H, 1.64; N, 11.50); tlc (ethyl acetate) Rf 0.59.

4-Chloro-6-iodoquinazoline was prepared from 5-iodoanthranilic acid as follows:
5-Iodoanthranilic acid (Aldrich) (5.0g, 19mmol and formamidine acetate (10g, 96mmol) were reacted in glacial acetic acid (40ml) at reflux for 2 hours. The reaction mixture was concentrated under vacuum and water added to form a precipitate. This was collected by filtration and dried at 60°C under vacuum to give 4-hydroxy-6-

iodoquinazoline as a brown solid (4.5g, 87%); δH [$^2H_6$] -DMSO 12.32 (1H, b, OH), 8.40 (1H, s, 2-H), 8.10 (2H, m, 5-H, 7-H), 7.46 (1H, d, 8-H).

4-Hydroxy-6-iodoquinazoline (1.9g, 7.0mmol), phosphorus oxychloride (5.2ml, 56mmol) and triethylamine (2.8ml, 20mmol) were reacted for 2.5 hours according to Procedure D to give 4-chloro-6-iodoquinazoline as a yellow solid (810mg, 40%), which was used without further purification.

4-Chloro-6-trifluoromethoxyquinazoline

4-Hydroxy-6-trifluoromethoxyquinazoline (Maybridge) (0.500g, 2.2mmol), phosphorus oxychloride (1.6ml, 17mmol) and triethylamine (0.7ml, 5.0mmol) were reacted for 1.5 hours according to Procedure D to give 4-chloro-6-trifluoromethoxyquinazoline as a colourless oil (0.380g, 70%), which was used without further characterisation.

4-Chloro-7-(trifluoromethyl)quinazoline was prepared from 2-nitro-4-(trifluoromethyl)benzonitrile as follows:

2-Nitro-4-(trifluoromethyl)benzonitrile (Aldrich) (1.0g, 4.63mmol), dissolved in DMSO (2.5ml) was cooled to 0°C, and treated with hydrogen peroxide solution (30%, 3ml) and then potassium carbonate (0.125g, 0.9mmol). The reaction stirred at ambient temperature for 1 hour, giving a precipitate. This was collected by filtration and dried at 60°C under vacuum to give 2-nitro-4-(trifluoromethyl)benzamide as a yellow solid (910mg, 84%); δH [$^2H_6$] -DMSO .8.38 (1H, s, 3-H), 8.26-8.07 (2H, m, 5-H, CONH), 7.85 (1H, d, 6-H), 7.31 (1H, b, CONH).

2-Nitro-4-(trifluoromethyl)benzamide (0.900g, 3.8mmol) was added to a boiling solution of ferrous sulphate heptahydrate (7g) in water (100ml) and the solution heated to reflux for 30 minutes. .880 ammonia (15ml) was then added and the heating continued for 20 minutes. The cooled reaction was filtered and the residue extracted with hot ethanol. The ethanol extracts were concentrated under vacuum, and the residue washed with water and dried at 60°C under vacuum to give 4-(trifluoromethyl)anthranilamide as a yellow solid (300mg, 38%); δH [$^2H_6$] -DMSO 7.81 (1H, b, CONH), 7.69 (1H, d), 7.27 (1H, b, CONH), 7.00 (1H, s, 3-H), 6.81 (2H, s, NH_2), 6.73 (1H, d).

4-(Trifluoromethyl)anthranilamide (0.150g, 0.73mmol) was reacted with formic acid (0.5ml, 13mmol) at reflux for 2.5 hours. After cooling the reaction was diluted with acetone, and the resulting precipitated collected by filtration and washed with acetone to give 4-hydroxy-7-(trifluoromethyl)quinazoline as an off-white solid (0.120g, 76%); δH [$^2H_6$] -DMSO 12.43 (1H, b, OH), 8.31 (1H, d, 5-H), 8.20 (1H, s, 2-H), 7.95 (1H, s, 8-H), 7.80 (1H, d, 6-H).

4-Hydroxy-7-(trifluoromethyl)quinazoline (0.120g, 0.56mmol), phosphorus oxychloride (0.5ml, 5.4mmol) and triethylamine (0.25ml, 1.8mmol) were reacted at reflux under nitrogen for 2.5 hours. The excess reagents were removed at 70°C under vacuum. The residue was extracted with boiling heptane (250ml) containing 5% triethylamine. The extract was allowed to cool and washed with aqueous ammonium chloride solution and water. The organic phase was dried ($MgSO_4$) and concentrated under vacuum to give 4-chloro-7-(trifluoromethyl)quinazoline as a yellow solid (0.100g, 77%); δH [$^2H_6$] -DMSO 8.30 (2H, m, 2-H, 5-H), 7.98 (1H, s, 8-H), 7.80 (1H, d, 6-H).

4-Chloro-6-nitroquinazoline was prepared from 5-nitroanthrnilic acid as follows:
5-Nitroanthranilic acid (Aldrich) (15g, 82mmol) and formamidine acetate (30g, 288mmol) in glacial acetic acid (100ml) were heated to reflux for 4 hours. The reaction mixture was concentrated under vacuum and then diluted with water. The precipitate formed was filtered off and dried at 60°C to give 4-hydroxy-6-nitroquinazoline as a yellow solid (11.7g, 74%); δH [$^2H_6$] -DMSO 12.64 (1H, b, OH), 8.80 (1H, s, 5-H), 8.53 (1H, d, 7-H), 8.29 (1H, s, 2-H), 7.85 (1H, d, 8-H).
4-Hydroxy-6-nitroquinazoline (0.680g, 3.6mmol), phosphorus oxychloride (2.6ml, 28mmol) and triethylamine (1.1ml, 7.9mmol) were reacted for 2 hours according to Procedure D to give 4-chloro-6-nitroquinazoline as a yellow crystalline solid (0.290g, 39%); δH [$^2H_6$] -DMSO 8.80 (1H, s, 5-H), 8.55 (1H, d, 7-H), 8.35 (1H, s, 2-H), 7.87 (1H, d, 8-H).

4-Chloro-7-nitroquinazoline
7-Nitro-4-hydroxyquinazoline (prepared according to J. Org. Chem., 141-148, 1951) (3.1g, 16mmol), phosphorus oxychloride (12ml, 130mmol) and triethylamine (6ml, 43mmol) were reacted for 2 hours according to Procedure D. Recrystallisation from 60-80 petrol and drying at 40°C gave 4-chloro-7-nitroquinazoline as an orange solid (0.940g, 28%), which was used without further characterisation.

4-Chloro-6-methylthioquinazoline was prepared from 5-methylthioanthranilic acid as follows:
5-Methylthioanthranilic acid (J. Med. Chem., 26, 420-425, 1983) (1.0g, 5.5mmol) and formamide (6ml, 150mmol) were reacted at reflux for 1 hour. Water was added and the resulting precipitate collected by filtration and dried at 60°c under vacuum to give 4-hydroxy-6-methylthioquinazoline as an off-white solid (1.0g, 95%); δH [$^2H_6$] -DMSO 12.11 (1H, b, OH), 8.01 (1H, s, 2-H), 7.88 (1H, s, 5-H), 7.70 (1H, d, 7-H), 7.60 (1H, d, 8-H), 2.55 (3H, s, CH_3).

4-Hydroxy-6-methylthioquinazoline (1.0g, 5.2mmol), phosphorus oxychloride (4.0ml, 43mmol) and triethylamine (1.8ml, 13mmol) were reacted for 30 min according to Procedure D to give 4-chloro-6-methylthioquinazoline as a yellow solid (0.580g, 53%).

4-Chloro-6,7-diethoxyquinazoline

4-Chloro-6,7-diethoxyquinazoline was prepared from methyl 2-amino-4,5-diethoxybenzoate as follows:

A mixture of methyl 2-amino-4,5-diethoxybenzoate (Salor *via* Aldrich) (2.27g; 9.5 mmol), formamidine acetate (6.8 g; 65 mmol) and glacial acetic acid (38 ml) was heated at reflux under nitrogen for 5 hours. The hot mixture was poured onto ice (110 g), and the pale tan solution stood at 0°C for 18 hours. The off-white solid that formed was collected by filtration, washed with cold water and dried to give 6,7-diethoxy-4-hydroxyquinazoline hemiacetate as an off-white powder (1.82 g, 82%) with mp 253-255°C; (Found C, 59.00; H, 5.97; N, 10.68. $C_{12}H_{14}N_2O_3.0.5CH_3CO_2H$ requires C, 59.09; H, 6.06; N, 10.60); tlc (ethyl acetate) Rf 0.13.

A mixture of 6,7-diethoxy-4-hydroxyquinazoline hemiacetate (2.64 g; 10 mmol), thionyl chloride (25 ml) and dimethylformamide (3 drops) was heated at reflux under nitrogen for 4 hours, cooled to 30°C and evaporated *in vacuo*. The tan residue was dissolved in ethyl acetate (50 ml) and the solution extracted with 5% aqueous potassium hydrogen carbonate (3 x 20 ml) and water (2 x 20 ml), dried (Na_2SO_4), filtered and evaporated to dryness to give a tan solid (2.61 g). Crystallisation from 30% cyclohexane in ethyl acetate afforded 4-chloro-6,7-diethoxyquinazoline (1.77 g, 70%) as pale yellow-tan needles with mp 140-141°C; (Found C, 56.96; H, 5.13; N, 10.85. $C_{12}H_{13}ClN_2O_2$ requires C, 57.03; N, 5.15; N, 11.09); tlc (ethyl acetate) Rf 0.49.

4-Chloro-6,7-methylenedioxyquinazoline

4-Chloro-6,7-methylenedioxyquinazoline was prepared from 2-nitropiperonal as follows:

Silver oxide suspension was prepared by treating a solution of silver nitrate (6.64 g; 40 mmol) in water (100 ml) with 10 M sodium hydroxide (6 ml; 60 mmol). To a well stirred suspension of silver oxide was added a hot (70°C) solution of 2-nitropiperonal (Aldrich) (4.0 g; 20 mmol) in ethanol (100 ml) over 30 minutes. When the addition was complete, the mixture was stirred vigorously for 3 hours at 40°C, and then at 90°C for 10 minutes. Metallic silver was removed by filtration and the tan filtrate was evaporated to two-thirds volume, cooled to 10°C and acidified (pH1) with 50% sulphuric acid. On standing at 0°C for several hours, yellow prisms were deposited. The 2-nitro-4,5-methylenedioxy benzoic acid was collected by filtration, washed with

cold water and dried to give a yellow crystalline solid (3.64 g, 86%) with mp 170-171°C; (Found C, 44.77; H, 2.35; N, 6.27. $C_8H_5NO_6.0.25\ H_2O$ requires C, 44.56; H, 2.55; N, 6.49); tlc (ethyl acetate) Rf 0.10.

A mixture of 2-nitro-4,5-methylenedioxy benzoic acid (3.64 g; 17.25 mmol), thionyl chloride (7 ml) and dry chloroform (40 ml) was heated at reflux for 45 minutes and evaporated to dryness *in vacuo* to give 2-nitro-4,5-methylenedioxy benzoyl chloride as a tan oil. The 2-nitro-4,5-methylenedioxy benzoyl chloride was treated with dry methanol (40 ml) and the mixture stirred at 18°C for 24 hours and then allowed to stand at 0°C for 18 hours. The sand coloured solid was collected by filtration, washed with cold (-10°C) methanol and dried to give methyl 2-nitro-4,5-methylenedioxy benzoate (3.48g, 88%) with mp 101-102°C; (Found C, 48.03; H, 3.21; N, 6.13. $C_9H_7NO_6$ requires C, 48.00; H, 3.11; N, 6.22); tlc (ethyl acetate) Rf 0.60.

A mixture of methyl 2-nitro-4,5-methylenedioxy benzoate (1.125 g; 5.0 mmol) and 10% palladium on carbon (0.25 g) in methanol (50 ml) was hydrogenated at room temperature and pressure until 336 ml hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate evaporated to one quarter of its original volume. On standing, colourless prisms were deposited. The methyl 2-amino-4,5-methylenedioxy benzoate was collected by filtration, washed with cold (-5°C) methanol and dried to give a colourless solid (0.930 g, 95%) with mp 103-104°C; (Found C, 55.13; H, 4.42; N, 7.09. $C_9H_9NO_4$ requires C,55.38; H, 4.61; N, 7.18); tlc (ethyl acetate) Rf 0.62.

A mixture of methyl 2-amino-4,5-methylenedioxybenzoate (1.24 g; 6.33 mmol), formamidine acetate (4.5 g; 43.3 mmol) and glacial acetic acid (25 ml) was heated at reflux for 6.5 hours. The hot mixture was poured onto crushed ice (70 g) to precipitate the product, which was collected by filtration, washed with water and dissolved in 2M aqueous sodium hydroxide (5 ml). After removing a small quantity of insoluble material by filtration, the straw coloured solution was adicified (pH3) with acetic acid. The off-white prisms deposited were collected by filtration, washed with water and dried to give 4-hydroxy-6,7-methylenedioxyquinazoline hemi-acetate as a pale grey powder (1.06 g, 88%) with mp 311-314°C (dec.); (Found C, 54.31; H, 3.71; N, 12.66. $C_9H_6N_2O_3.0.5CH_3CO_2H$ requires C, 54.54; H, 3.63; N, 12.72); tlc (10% methanol-ethyl acetate) Rf 0.42.

A mixture of 4-hydroxy-6,7-methylenedioxyquinazoline hemi-acetate (1.10 g; 5.0 mmol), thionyl chloride (12.5 ml) and dimethylformamide (2 drops) under nitrogen was heated at reflux for 4.5 hours, cooled to 40°C and evaporated *in vacuo*. The yellow residue was evaporated twice more with ethyl acetate (20 ml) and then suspended in cold (-5°C) ethyl acetate. The vigorously stirred suspension was treated with cold (0°C)

5% aqueous potassium hydrogen carbonate solution (20 ml) and the phases separated when no solid remained. The organic layer was washed with cold 5% potassium hydrogen carbonate solution (2 x 20 ml), dried over sodium sulphate, filtered and evaporated to dryness. Crystallisation of the pale yellow residue from 30% cyclohexane-ethyl acetate afforded 4-chloro-6,7-methylenedioxyquinazoline as fine, very pale yellow needles (1.01 g, 90%) with mp 167-168°C; (Found C, 51.76; H, 2.29; N, 13.59. $C_9H_5ClN_2O_2$ requires C, 51.80; H, 2.40; N, 13.43); tlc (ethyl acetate) Rf 0.54.

4-Chloro-6,7-dimethoxy-2-methylquinazoline

4-Chloro-6,7-dimethoxy-2-methylquinazoline was prepared from 2-amino-4,5-dimethoxy benzoic acid as follows:

An mixture of 2-amino-4,5-dimethoxy benzoic acid (3.94 g; 20 mmol) and thioacetamide (2.25 g; 30 mmol) was heated at 140-145°C for 2.5 hours and then at 155-160°C for 30 minutes. After cooling, the dark mass was treated with water (30 ml) and the mixture stirred for 1 hour. The precipitated solid was filtered off, washed with 5% aqueous potassium bicarbonate and water, and dried *in vacuo* at 65°C. Crystallisation from acetic acid afforded 4-hydroxy-6,7-dimethoxy-2-methylquinazoline as pale grey plates (3.32 g, 76%) with mp 308-310°C (sublimes at 300°C); (Found C, 59.88; H, 5.48; N, 12.49. $C_{11}H_{12}N_2O_3$ requires C, 60.00; H, 5.45; N, 12.73); tlc (10% methanol in ethyl acetate) Rf 0.36.

4-Hydroxy-6,7-dimethoxy-2-methylquinazoline (1.10 g; 5.0 mmol), thionyl chloride (12.5 ml) and dimethylformamide (2 drops) were heated at reflux under nitrogen for 7.5 hours. The mixture was evaporated to dryness and the pale yellow residue suspended in cold (-2°C) ethyl acetate (50 ml) and treated with cold (0°C) 5% aqueous potassium bicarbonate (30 ml). After stirring vigorously until no solid remained, the phases were separated and the organic layer dried over sodium sulphate, filtered and evaporated to give a pale yellow solid (1.10 g). Crystallisation from 30% cyclohexane-ethyl acetate gave the product (0.920 g; 77%) as fine cream needles with mp 175-177°C; (Found C, 55.25; H, 4.76; N, 11.59. $C_{11}H_{11}ClN_2O_2$ requires C, 55.34; H, 4.61; N, 11.72); tlc (ethyl acetate) Rf 0.40.

The synthesis of other intermediates is described with the relevant examples. If an intermediate is commercially available the supplier name is given in backets.

3-Phenoxyaniline and 4-phenoxyaniline are available from Aldrich.

4-Benzyloxyaniline is available from Aldrich as the hydrochloride salt; this is treated with aqueous sodium hydrogen carbonate solution, and the mixture extracted with ethyl

acetate; the organic solution is dried ($MgSO_4$) and concentrated to give the free base as a brown solid, used without further purification.

Examples

Example 1

4-(3-Phenoxyanilino)quinoline hydrochloride

4-Chloroquinoline (0.280g, 1.72 mmol) and 3-phenoxyaniline (0.317g, 1.72 mmol) were reacted in 2-propanol (8 ml) for 3 hours according to Procedure A. The yellow crystalline solid thus obtained was recrystallised from 2-propanol to give the product as yellow crystals with mp 218°C ; (Found: C, 71.67; H, 4.73 N, 8.24; Cl, 12.06. $C_{21}H_{16}N_2O.1.15HCl$ requires: C, 71.19; H, 4.88; N, 7.91; Cl, 11.51%); δH [$^2H_6$]-DMSO 10.85 (1H, br s, NH), 8.71 (1H, d, J 8, 2-H), 8.55 (1H, d, J 6.5, 8-H), 8.00-8.06 (2H, m, 5-H, 7-H), 7.75-7.85 (1H, m, 6-H), 7.58 (1H, t, J 8, 5'-H), 7.45 (2H, t, J 7.5, 3"-H, 5"-H), 7.01-7.30 (6H, m, 2'-H, 4'-H, 6'-H, 2"-H, 4"-H, 6"-H), 6.94 (1H, d, J 8.5, 3-H); m/z (%) 313 (100, $M+1^+$).

Example 2

6,7-Dimethoxy-4-(3-phenoxyanilino)quinoline hydrochloride

4-Chloro-6,7-dimethoxyquinoline (0.300g, 1.34 mmol) and 3-phenoxyaniline (0.322g, 1.74 mmol) were reacted in DMF (6 ml) for 4.5 hours at 140°C according to Procedure B. The product was thus obtained as a cream solid (0.360g, 66%) with mp 248°C ; (Found: C, 67.69; H, 5.22 N, 6.81. $C_{23}H_{20}N_2O_3.HCl$ requires: C, 67.70; H, 5.18; N, 6.86%); δH [$^2H_6$]-DMSO 10.75 (1H, br s, NH), 8.34 (1H, d, J 7, 2-H), 8.19 (1H, s, 8-H), 7.50-7.58 (2H, m, 5-H, 5'-H), 7.39-7.49 (2H, t, J 8, 3"-H, 5"-H), 6.95-7.30 (6H, m, 2'-H, 4'-H, 6'-H, 2"-H, 4"-H, 6"-H), 6.83 (1H, d, J 8.5, 3-H), 4.02 and 3.99 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 373 (100, $M+1^+$).

Example 3

4-(4-Phenoxyanilino)quinoline hydrochloride

4-Chloroquinoline (0.110g, 0.672 mmol) and 4-phenoxyaniline (0.125g, 0.675 mmol) were reacted in 2-propanol (4 ml) for 2.5 hours according to Procedure B. The yellow crystalline solid thus obtained was dried at 60°C to give the product (0.200g, 84%) with mp 216-218°C ; (Found: C, 71.21; H, 4.84 N, 7.66. $C_{21}H_{16}N_2O.HCl.0.3H_2O$ requires: C, 71.20; H, 5.01; N, 7.91%); δH [$^2H_6$]-DMSO 14.69 (1H, v br s, HCl), 11.01 (1H, br s, NH), 8.87 (1H, d, J 9, 2-H), 8.52 (1H, d, J 8, 8-H), 7.98-8.19 (2H, m, 5-H, 7-H), 7.82 (1H, t, J 8, 6-H), 7.40-7.58 (4H, m, 2'-H,

6'-H, 3"-H, 5"-H), 7.08-7.27 (5H, m, 3'-H, 5'-H, 2"-H, 4"-H, 6"-H), 6.78 (1H, d, J 8, 3-H); m/z (%) 312 (100, M^+); ν_{max} (KBr disc)/cm^{-1} 1614, 1591, 1539, 1499, 1450, 1244, 1223.

Example 4

6,7-Dimethoxy-4-(4-phenoxyanilino)quinoline hydrochloride

6,7-Dimethoxy-4-chloroquinoline (0.150g, 0.671 mmol) and 4-phenoxyaniline (0.250g, 1.35 mmol) were reacted in 2-propanol (4 ml) for 1.5 hours according to Procedure B. The yellow crystalline solid thus obtained was dried at 60°C to give the product (0.210g, 74%) with mp 226-229°C (decomp); (Found: C, 65.35; H, 5.02 N, 6.53. $C_{23}H_{20}N_2O_3.HCl.0.75H_2O$ requires: C, 65.40; H, 5.37; N, 6.63%); δH [$^2H_6$]-DMSO 10.49 (1H, br s, NH), 8.31 (1H, d, J 7, 2-H), 8.11 (1H, s, 8-H), 7.39-7.50 (5H, m, 5-H, 2'-H, 6'-H, 3"-H, 5"-H), 7.13-7.25 (3H, m, 2"-H, 4"-H, 6"-H), 7.09 (2H, d, J, 9, 3'-H, 5'-H), 6.70 (1H, d, J 7, 3-H), 3.99 and 3.97 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 372 (100, M^+); ν_{max} (KBr disc)/cm^{-1} 1603, 1504, 1487, 1471, 1230.

Example 5

4-(3-Benzyloxyanilino)quinoline hydrochloride

4-Chloroquinoline (0.280g, 1.72 mmol) and 3-benzyloxyaniline (0.338g, 1.72 mmol) were reacted in 2-propanol (8 ml) for 3 hours according to Procedure B. Recrystallisation from 2-propanol gave the product as a yellow crystalline solid (0.128g, 18%), with mp 237°C; (Found: C, 63.63; H, 4.38 N, 6.63; Cl, 12.76. $C_{22}H_{18}N_2O.1.5HCl.2H_2O$ requires: C, 63.19; H, 5.86; N, 6.70; Cl, 12.74%); δH [$^2H_6$]-DMSO 10.94 (1H, br s, NH), 8.80 (1H, d, J 9, 8-H), 8.51 (1H, d, J 6, 2-H), 7.97-8.15 (2H, m, 5-H, 7-H), 7.83 (1H, t, J 7.5, 6-H), 7.30-7.60 (6H, m, 5'-H, 5 x PhH), 7.13-7.23 (3H, m, 2'-H, 4'-H, 6'-H), 6.34 (1H, d, J 6, 3-H), 5.19 (2H, s, CH_2); m/z (%) 326 (99, M^+), 91 (100).

Example 6

4-(4-Benzyloxyanilino)quinoline hydrochloride

4-Chloroquinoline (0.100g, 0.611 mmol) and 4-benzyloxyaniline (0.120g, 0.603 mmol) were reacted in 2-propanol (4 ml) for 3 hour according to Procedure A. The yellow solid thus obtained was the product (0.180g, 82%). A portion was recrystallised from hot 2-propanol to give a yellow crystalline solid with mp 250-252°C; (Found: C, 72.47; H, 5.35 N, 7.57. $C_{22}H_{18}N_2O.HCl$ requires: C, 72.82; H, 5.28; N, 7.72%); δH [$^2H_6$]-DMSO 10.89 (1H, br s, NH), 8.79 (1H, d, J 9, 8-H),

8.49 (1H, d, J 7, 2-H), 7.99-8.13 (2H, m, 5-H, 7-H), 7.80 (1H, t, J 7.5, 6-H), 7.42-7.53 (7H, m, 2'-H, 6'-H, 5 x PhH), 7.22 (2H, d, J 9, 3'-H, 5'-H), 6.18 (1H, d, J 7, 3-H), 5.19 (2H, s, CH_2); m/z (%) 326 (26, M^+), 235 (100), 88 (39); ν_{max} (KBr disc)/cm^{-1} 1618, 1601, 1543, 1508, 1227.

Example 7

4-(4-Benzyloxyanilino)-6,7-dimethoxyquinoline hydrochloride

6,7-Dimethoxy-4-chloroquinoline (0.500g, 2.24 mmol) and 4-benzyloxyaniline (0.450g, 2.26 mmol) were reacted in 2-propanol (10 ml) for 4 hours according to Procedure A, but TLC still showed remaining starting materials. Further 4-benzyloxyaniline (0.450g, 2.26 mmol) was added and the mixture was heated to reflux for 1 hour. The yellow crystalline solid thus obtained was dried at 60°C to give the product (0.290g, 31%) with mp 245-248°C (decomp); (Found: C, 68.03; H, 5.45 N, 6.57. $C_{24}H_{22}N_2O_3.HCl$ requires: C, 68.16; H, 5.48; N, 6.62%); δH [$^2H_6$]-DMSO 10.64 (1H, br s, NH), 8.30 (1H, d, J 6, 2-H), 8.18 (1H, s, 8-H), 7.30-7.55 (8H, m, 5-H, 2'-H, 6'-H, 5 x PhH), 7.18 (2H, d, J, 9.5, 3'-H, 5'-H), 6.59 (1H, d, J 6, 3-H), 5.19 (2H, s, CH_2), 4.01 and 3.99 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 387 (100, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1508, 1232.

Example 8

5-Chloro-2-[2-methyl-4-(4-quinolylamino)phenyl]isoindol-1,3-dione hydrochloride

4-Chloroquinoline (0.380g, 2.33 mmol) and N-(4-amino-2-methylphenyl)-4-chlorophthalimide (0.668g, 2.33 mmol) were reacted in 2-propanol (16 ml) for 6 hours according to Procedure B. The solid thus obtained was purified by column chromatography on silica, eluting with chloroform/methanol (9:1) to give the product as yellow crystals with mp 278°C; (Found: C, 64.20; H, 4.00 N, 9.11. $C_{24}H_{16}N_3O_2Cl.HCl$ requires: C, 64.01; H, 3.80; N, 9.33%); δH [$^2H_6$]-DMSO 9.10 (1H, br s, NH), 8.55 (1H, d, J 5.5, 2"-H), 8.40 (1H, d, J 7.5, 8"-H), 7.88-8.10 (4H, m, 3-H, 6-H, 7-H, 5"-H), 7.75 (1H, t, J 7.5, 7"-H), 7.59 (1H, t, 7.5, 6"-H), 7.30-7.45 (3H, m, 3'-H, 5'-H, 6'-H), 7.14 (1H, d, J 5.5, 3"-H), 2.15 (3H, s, CH_3); m/z (%) 414 (100, $M+1^+$).

Example 9

5-Chloro-2-[4-(6,7-dimethoxy-4-quinolylamino)-2-methylphenyl]isoindol-1,3-dione hydrochloride

4-Chloro-6,7-dimethoxyquinoline (0.300g, 1.34 mmol) and N-(4-amino-2-methylphenyl)-4-chlorophthalimide (0.499g, 1.74 mmol) were reacted in DMF (6

ml) for 4.5 hours at 140°C according to Procedure B. The product was thus obtained as a white solid (0.185g, 27%), with mp 295°C: (Found: C, 60.67; H, 4.06 N, 8.12. $C_{26}H_{20}N_3O_4Cl.1.1HCl$ requires: C, 60.70; H, 3.92; N, 8.17%); δH [$^2H_6$]-DMSO 10.54 (1H, br s, NH), 8.29 (1H, d, J 5.5, 2"-H), 7.88-8.15 (4H, m, 3-H, 6-H, 7-H, 8"-H), 7.40-7.52 (4H, m, 3'-H, 5'-H, 6'-H, 5"-H), 6.93 (1H, d, J 5.5, 3"-H), 4.07 and 4.04 (2 x 3H, 2 x s, 2 x OCH_3), 2.24 (3H, s, CH_3); m/z (%) 473 (100, M^+).

Example 10

4-(4-Benzyloxyanilino)-2-methylquinoline hydrochloride and free base

4-Chloroquinaldine (4-chloro-2-methylquinoline) (Aldrich) (0.360g, 2.03 mmol) and 4-benzyloxyaniline (0.497g, 2.49 mmol) were reacted in 2-propanol (20 ml) for 48 hours according to Procedure B. The product was thus obtained as a yellow crystalline solid (0.738g, 94%), which decomposed above 270°C; (Found: C, 71.10; H, 5.49 N, 7.16. $C_{23}H_{20}N_2O.HCl.0.6H_2O$ requires: C, 71.25; H, 5.77; N, 7.23%); δH [$^2H_6$]-DMSO 10.57 (1H, br s, NH), 8.70 (1H, d, J 9. 8-H), 8.03 (1H, d, J 9, 5-H), 7.98 (1H, t, J 8.5, 7-H), 7.74 (1H, t, J 8.5, 6-H), 7.49 (2H, d, J 8, 2'-H, 6'-H), 7.30-7.46 (5H, m, 5 x PhH), 7.20 (2H, d, J 9, 3'-H, 5'-H), 6.55 (1H, s, 3-H), 5.18 (2H, s, CH_2), 2.59 (3H, s, 2-CH_3); m/z (%) 340 (25, M^+), 249 (100); ν_{max} (KBr disc)/cm^{-1} 1608, 1595, 1558, 1506, 1454.

4-(4-Benzyloxyanilino)-2-methylquinoline hydrochloride (0.603g, 1.60 mmol) was treated with excess triethylamine. The resulting yellow slurry was partioned between ethyl acetate and water, and the aqueous layer extracted with further ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give the free base of the product as a yellow solid (0.530g, 80%), with mp 210-212°C; (Found: C, 81.02; H, 5.87 N, 8.11. $C_{23}H_{20}N_2O$ requires: C, 81.15; H, 5.92; N, 8.23%); δH [$^2H_6$]-DMSO 8.60 (1H, br s, NH), 8.30 (1H, d, J 9, 8-H), 7.75 (1H, d, J 9, 5-H), 7.61 (1H, t, J 8, 7-H), 7.31-7.50 (5H, m, 6-H, 5 x PhH), 7.28 (2H, d, J 9, 2'-H, 6'-H), 7.08 (2H, d, J 9, 3'-H, 5'-H), 6.53 (1H, s, 3-H), 5.11 (2H, s, CH_2), 2.39 (3H, s, 2-CH_3); m/z (%) 340 (18, M^+), 249 (100), 91 (22); ν_{max} (KBr disc)/cm^{-1} 1585, 1510.

Example 11

4-(4-Phenoxyanilino)-2-methylquinoline hydrochloride

4-Chloroquinaldine (4-chloro-2-methylquinoline) (Aldrich) (0.191g, 1.08 mmol) and 4-phenoxyaniline (0.222g, 1.20 mmol) were reacted in 2-propanol (10 ml) for 14 hours according to Procedure B. The product was thus obtained as a yellow solid (0.341g, 87%), with mp 208-210°C; (Found: C, 73.07; H, 5.39 N, 7.67.

$C_{22}H_{18}N_2O.HCl$ requires: C, 72.82; H, 5.28; N, 7.72%); δH [$^2H_6$]-DMSO 10.68 (1H, br s, NH), 8.73 (1H, d, J 9, 8-H), 8.05 (1H, d, J 8.5, 5-H), 7.98 (1H, t, J 8, 7-H), 7.74 (1H, t, J 8.5, 6-H), 7.40-7.50 (4H, m, 2'-H, 6'-H, 3"-H, 5"-H), 7.14-7.23 (3H, m, 2"-H, 4"-H, 6"-H), 7.12 (2H, d, J 9, 3'-H, 5'-H), 6.69 (1H, s, 3-H), 2.63 (3H, s, 2-CH_3); m/z (%) 326 (100, M^+); ν_{max} (KBr disc)/cm^{-1} 1599, 1487, 1221.

Example 12

4-(4-Benzyloxyphenoxy)quinazoline

4-Chloroquinazoline (0.165g, 1.00 mmol), 4-benzyloxyphenol (0.240g, 1.20 mmol) and potassium carbonate (0.166g, 1.20 mmol) were stirred in acetone (5 ml) and heated to reflux for 4 hours, and then left to stand overnight. The reaction mixture was filtered, and the filtrate concentrated. Column chromatography on silica, eluting with ethyl acetate/petrol (gradient elution, 20% - 50%), gave the product as a white crystalline solid (0.294g, 90%), with mp 104-106°C; (Found: C, 76.70; H, 4.95 N, 8.29. $C_{21}H_{16}N_2O_2$ requires: C, 76.81; H, 4.91; N, 8.53%); δH [$^2H_6$]-DMSO 8.71 (1H, s, 2-H), 8.38 (1H, d, J 9, 8-H), 7.96-8.08 (2H, m, 5-H, 7-H), 7.79 (1H, t, J 7, 6-H), 7.50 (2H, d, J 7, 2"-H, 6"-H), 7.44 (2H, t, J 7.5, 3"-H, 5"-H), 7.35 (1H, t, J 7.5, 4"-H), 7.28 (2H, d, J 10, 2'-H, 6'-H), 7.13 (2H, d, J 9.5, 3'-H, 5'-H), 5.15 (2H, s, CH_2); m/z (%) 328 (66, M^+), 129 (75), 102 (74), 91 (100); ν_{max} (KBr disc)/cm^{-1} 1508, 1491, 1385, 1203.

Example 13

4-(4-Benzyloxyphenoxy)-6,7-dimethoxyquinazoline

4-Chloro-6,7-dimethoxyquinazoline (0.225g, 1.00 mmol), 4-benzyloxyphenol (0.240g, 1.20 mmol) and potassium carbonate (0.160g, 1.16 mmol) were stirred in acetone (10 ml) and heated to reflux for 8 hours, and then left to stand overnight. Further 4-benzyloxyphenol (0.100g, 0.50 mmol) and potassium carbonate (0.075g, 0.54 mmol) were added and the mixture heated to reflux for a further 8 hours and again left at room temperature overnight. The reaction mixture was filtered, and the filtrate concentrated. Column chromatography on silica, eluting with ethyl acetate/petrol (gradient elution, 25% - 75%), followed by recrystallisation from ethyl acetate gave the product as a white crystalline solid (0.355g, 91%), with mp 176-178°C; (Found: C, 71.03; H, 5.28 N, 7.11. $C_{23}H_{20}N_2O_4$ requires: C, 71.12; H, 5.19; N, 7.21%); δH [$^2H_6$]-DMSO 8.76 (1H, s, 2-H), 7.78 (1H, s, 8-H), 7.69-7.75 (2H, m, 2"-H, 6"-H), 7.54-7.68 (4H, m, 5-H, 3"-H, 4"-H, 5"-H), 7.45 (2H, d, J 9, 2'-H, 6'-H), 7.30 (2H, d, J 9, 3'-H, 5'-H), 5.37 (2H, s, CH_2), 4.21 and 4.19 (2 x 3H, 2 x

s, 2 x OCH_3); m/z (%) 388 (92, M^+), 189 (100); ν_{max} (KBr disc)/cm^{-1} 1506, 1381, 1234, 1207.

Example 14

4-[(4-Benzylmercapto)phenoxy]quinazoline

4-Hydroxythiophenol (2.66g, 21.08 mmol), potassium carbonate (3.205g, 23.19 mmol) and benzyl bromide (2.5 ml, 3.60g, 21.02 mmol) were dissolved in acetone under a nitrogen atmosphere, heated to reflux with stirring for 3 hours, and then stirred at room temperature overnight. The mixture was filtered to remove inorganics, washing with excess DCM, and the filtrate and washings concentrated in vacuo. Column chromatography on silica, eluting with ethyl acetate/toluene (gradient elution, 5% -10%), gave 4-benzylmercaptophenol as a cream solid (3.32g, 73%). Recrystallisation of a portion from ether/petrol gave cream crystals with mp 100-102°C; (Found: C, 72.33; H, 5.53. $C_{13}H_{12}OS$ requires: C, 72.19; H, 5.59%); δH [$^2H_6$]-DMSO 9.42 (1H, br s, O-H), 7.10-7.28 (7H, m, 3-H, 5-H, 5 x PhH), 6.69 (2H, d, J 9, 2-H, 6-H), 4.02 (2H, s, CH_2); m/z (%) 216 (43, M^+), 91 (100); ν_{max} (KBr disc)/cm^{-1} 1495, 1257, 818.

4-Chloroquinazoline (0.166g, 1.01 mmol), 4-benzylmercaptophenol (0.238g, 1.10 mmol) and potassium carbonate (0.154g, 1.10 mmol) were stirred in acetone (10 ml) under a nitrogen atmosphere, and heated to reflux for a total of 12 hours. The reaction mixture was filtered, washing with excess acetone, and the combined filtrate and washings concentrated to a yellow solid. Column chromatography on silica, eluting with ethyl acetate/petrol (gradient elution, 20% - 25%), gave the product as a cream solid (0.285g, 82%). Recrystallisation of a portion from ethyl acetate/petrol gave a white crystalline solid with mp 148-149°C; (Found: C, 73.02; H, 4.66 N, 7.98. $C_{21}H_{16}N_2OS$ requires: C, 73.23; H, 4.68; N, 8.13%); δH [$^2H_6$]-DMSO 8.72 (1H, s, 2-H), 8.38 (1H, d, J 9, 8-H), 7.95-8.09 (2H, m, 5-H, 7-H), 7.79 (1H, t, J 8, 6-H), 7.47 (2H, d, J 7, 3'-H, 5'-H), 7.22-7.42 (7H, m, 2'-H, 6'-H, 5 x PhH), 4.28 (2H, s, CH_2); m/z (%) 344 (56, M^+), 91 (100); ν_{max} (KBr disc)/cm^{-1} 1485, 1375.

Example 15

4-[(4-Benzylmercapto)phenoxy]-6,7-dimethoxyquinazoline

4-Chloro-6,7-dimethoxyquinazoline (0.225g, 1.00 mmol), 4-benzylmercaptophenol (0.240g, 1.11 mmol) and potassium carbonate (0.152g, 1.10 mmol) were stirred in acetone (10 ml) under a nitrogen atmosphere, and heated to reflux for a total of 16 hours. Tlc showed remaining quinazoline and phenolic starting materials so further

potassium carbonate (0.04g, 0.30 mmol) was added and the mixture heated to reflux for a further 7 hours. The reaction mixture was filtered, washing with excess acetone, and the combined filtrate and washings concentrated to a white solid. Column chromatography on silica, eluting with ethyl acetate/petrol (gradient elution, 75% - 90%), gave the product as a white solid (0.334g, 83%). Recrystallisation from ethyl acetate gave a white crystalline solid with mp 125-127oC; (Found: C, 68.09; H, 4.86 N, 6.90. $C_{23}H_{20}N_2O_3S$ requires: C, 68.30; H, 4.98; N, 6.93%); δH [$^2H_6$]-DMSO 8.55 (1H, s, 2-H), 7.54 (1H, s, 8-H), 7.46 (2H, d, J 9, 3'-H, 5'-H), 7.20-7.40 (8H, m, 5-H, 2'-H, 6'-H, 5 x PhH), 4.27 (2H, s, CH_2), 3.98 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 404 (20, M^+), 91 (100); ν_{max} (KBr disc)/cm^{-1} 1500, 1418, 1337, 1232, 1213.

Example 16

4-(4-Benzyloxyphenylmercapto)quinazoline

4-Hydroxythiophenol (0.66g, 5.23 mmol) was dissolved in acetonitrile (10 ml) with stirring and treated with iron (III)chloride (0.85g, 5.24 mmol), added as a suspension in acetonitrile (6 ml). The flask was then evacuated and flushed with nitrogen, and a nitrogen atmosphere maintained. Tributyl tin methoxide (1.5 ml, 1.67g, 5.21 mmol) was added dropwise via syringe, causing a gradual darkening of the solution, which was then stirred at room temperature overnight. The mixture was partioned between ethyl acetate and brine, and the latter layer extracted further (x2) with ethyl acetate. The combined organic solutions were dried ($MgSO_4$), and concentrated in vacuo to an orange oil. Column chromatography on silica, eluting with ethyl acetate/petrol (gradient elution, 20% - 50%), gave bis(4-hydroxyphenyl)disulphide contaminated with ca. 17% tributyl tin chloride, as a pale pink solid (0.703g of mixture, ca. 85% yield of disulphide); δH [$^2H_6$]-DMSO 9.73 (2H, s, 2 x OH), 7.29 (4H, d, J 9, 2 x 2-H, 2 x 6-H), 6.76 (2H, d, J 9, 2 x 3-H, 2 x 5-H), 1.55-1.67 (1.1H, m, 3 x $SnCH_2$), 1.28-1.39 (1.1H, m, 3 x $SnCH_2CH_2$), 1.08-1.18 (1.1H, m, 3 x $SnCH_2CH_2CH_2$), 0.89 (1.7H, t, J 8, 3 x CH_3); m/z (%) 250 (72, M^+), 125 (100); ν_{max} (KBr disc)/cm^{-1} 3323, 1585, 1493, 1223.

Bis(4-hydroxyphenyl)disulphide (containing tin impurity) (0.684g, ca. 0.57g of disulphide, 2.28 mmol) and potassium carbonate (0.691g, 5.00 mmol) were suspended in acetone under a nitrogen atmosphere, and stirred for 15 min at room temperature. Benzyl bromide (0.6 ml, 0.86g, 5.04 mmol) was then added and the mixture was heated to reflux for 5 hours, by which point tlc showed no remaining starting material. After standing overnight at room temperature, the mixture was filtered to remove inorganics, washing with excess acetone. The combined filtrate

and washings were concentrated to a cream solid. Column chromatography on silica, eluting with toluene/petrol (gradient elution, 10% - 70%), gave bis(4-benzyloxyphenyl)disulphide as a white solid (0.936g, 95%). A portion was recrystallised from tolene/petrol to give white crystals with mp 98-100°C; δH [$^2H_6$]-DMSO 7.28-7.50 (14H, m, 2 x 3-H, 2 x 5-H, 10 x PhH), 7.02 (4H, d, J 9, 2 x 2-H, 2 x 6-H), 5.10 (4H, s, 2 x CH_2); m/z (%) 430 (33, M^+), 91 (100); ν_{max} (KBr disc)/cm^{-1} 1599, 1493, 1242, 827; (Found: M^+ 430.1061, $C_{26}H_{22}ON_2S_2$ requires 430.1061).

Bis(4-benzyloxyphenyl)disulphide (0.129g, 0.30 mmol) was dissolved in freshly distilled THF (3 ml) with stirring under a nitrogen atmosphere. Lithium tri-tert-butoxyaluminohydride (1.0 molar in THF, 0.6 ml, 0.6 mmol) was added via syringe and the mixture was stirred at room temperature for 24 hours. The sulphide could not be isolated due to atmospheric re-oxidation. Therefore, further lithium tri-tert-butoxyaluminohydride (1.0 molar in THF, 0.6 ml, 0.6 mmol) was added, the mixture was stirred at room temperature for one hour, and then 4-chloroquinazoline (0.099g, 0.601 mmol) was added. The mixture was heated to reflux for a total of 1.5 hours, by which time tlc showed no remaining 4-chloroquinazoline. The mixture was partitioned between ethyl acetate and brine, and the aqueous extracted with further ethyl acetate (x 2) and DCM (x 2). The combined organic extracts were dried ($MgSO_4$), and concentrated in vacuo to an yellow gum. Column chromatography on silica, eluting with ethyl acetate/petrol (gradient elution, 10% - 20%), gave recovered disulphide starting material (0.041g, 32%), and the desired product, 4-(4-benzyloxyphenylmercapto)quinazoline, as a white solid (0.119g, 58%), with mp 132-134°C; (Found: C, 73.02; H, 4.68 N, 7.93. $C_{21}H_{16}N_2OS$ requires: C, 73.23; H, 4.68; N, 8.13%); δH [$^2H_6$]-DMSO 8.82 (1H, s, 2-H), 8.24 (1H, d, J 8.5, 8-H), 7.94-8.06 (2H, m, 5-H, 7-H), 7.79 (1H, t, J 8.5), 7.58 (2H, d, J 9, 2'-H, 6'-H), 7.49 (2H, d, J 8, 2"-H, 6"-H), 7.42 (2H, t, J 8, 3"-H, 5"-H), 7.32-7.39 (1H, m, 4"-H), 7.17 (2H, d, J 9, 3'-H, 5'-H), 5.19 (2H, s, CH_2); m/z (%) 344 (94, M^+), 253 (72), 129 (67), 102 (63), 91 (100); ν_{max} (KBr disc)/cm^{-1} 1485, 1321, 1244.

Example 17

4-(4-Benzyloxyphenylmercapto)-6,7-dimethoxyquinazoline

Bis(4-benzyloxyphenyl)disulphide (0.215g, 0.499 mmol) was dissolved in freshly distilled THF (5 ml) with stirring under a nitrogen atmosphere. Lithium tri-tert-butoxyaluminohydride (1.0 molar in THF, 1.2 ml, 1.2 mmol) was added via syringe and the mixture was stirred at room temperature for 3 hours. Further THF (5 ml)

and 4-chloro-6,7-dimethoxyquinazoline (0.224g, 0.997 mmol) were added, and the mixture was heated to reflux for a total of 3 hours, and then left at room temperature overnight. Tlc showed remaining disulphide and chloroquinazoline starting materials, so further lithium tri-tert-butoxyaluminohydride (1.0 molar in THF, 0.5 ml, 0.5 mmol) was added and the mixture stirred at room temperature for 1.5 hours. It was then heated to reflux for a further three hours, by which time tlc showed no remaining starting materials. The mixture was partitioned between ethyl acetate and brine, and the aqueous extracted with further ethyl acetate (x 2). The combined organic extracts were dried ($MgSO_4$), and concentrated in vacuo to a white solid. Column chromatography on silica, eluting with ethyl acetate/petrol (gradient elution, 20% - 90%), gave the desired product as a white crystalline solid (0.349g, 86%), with mp 175-177°C; (Found: C, 68.62; H, 4.89 N, 6.63. $C_{23}H_{20}N_2O_3S$ requires: C, 68.30; H, 4.98; N, 6.93%); δH [$^2H_6$]-DMSO 8.65 (1H, s, 2-H), 7.30-7.58 (9H, m, 5-H, 8-H, 2'-H, 6'-H, 5 x PhH), 7.24 (2H, d, J 9, 3'-H, 5'-H), 5.19 (2H, s, CH_2), 3.98 (6H, s, 2 x CH_3O); m/z (%) 404 (72, M^+), 313 (46), 91 (100); ν_{max} (KBr disc)/cm^{-1} 1508, 1244, 1163.

Example 18

4-(4-Benzyloxybenzyloxy)quinazoline

4-Benzyloxybenzyl alcohol (0.214g, 1.00 mmol) and sodium hydride (60% dispersion on mineral oil, 0.044g, ca.0.026g of NaH, 1.1 mmol) were suspended in freshly distilled THF (10 ml) under a nitrogen atmosphere and stirred at room temperature for 1.5 hours. 4-Chloroquinazoline (0.181g, 1.10 mmol) was added and the mixture was heated to reflux for 8 hours. TLC indicated that there was still benzyl alcohol present, so further sodium hydride (0.020g, ca. 0.012g of NaH, 0.5 mmol) was added and the mixture was heated to reflux for 3 hours more. The reaction mixture was filtered, washing with excess acetone, and the filtrate concentrated to a yellow solid. Column chromatography on silica, eluting with ethyl acetate/petrol (gradient elution, 10% - 25%), gave the product (0.180g, 53%). Recrystallisation of a portion from ethyl acetate gave a white crystalline solid with mp 85-87°C; (Found: C, 77.40; H, 5.39 N, 7.97. $C_{22}H_{18}N_2O_2$ requires: C, 77.19; H, 5.30; N, 8.18%); δH [$^2H_6$]-DMSO 8.81 (1H, s, 2-H), 8.16 (1H, d, J 8, 8-H), 7.82-8.00 (2H, m, 5-H, 7-H), 7.68 (1H, t, J 7.5, 6-H), 7.25-7.55 (7H, m, 2'-H, 6'-H, 5 x PhH), 7.05 (2H, d, J 9, 3'-H, 5'-H), 5.59 (2H, s, QuinOCH_2), 5.12 (2H, s, PhCH_2O); m/z (%) 342 (68, M^+), 197 (76), 91 (100); ν_{max} (KBr disc)/cm^{-1} 1572, 1495, 1414, 1346, 1240, 1232.

Example 19

4-(4-Benzyloxybenzyloxy)-6,7-dimethoxyquinazoline

4-Benzyloxybenzyl alcohol (0.129g, 0.60 mmol) and sodium hydride (60% dispersion on mineral oil, 0.024g, ca.0.014g of NaH, 0.60 mmol) were suspended in freshly distilled THF (5 ml) under a nitrogen atmosphere and stirred at room temperature for 45 min. 4-Chloro-6,7-dimethoxyquinazoline (0.112g, 0.498 mmol) was added stirring continued for 22 hours. TLC indicated that there was still chloroquinazoline starting material present, so further sodium hydride (0.020g, ca. 0.012g of NaH, 0.5 mmol) was added and stirring continued at room temperature for 48 hours. The reaction mixture was filtered, washing with excess ethyl acetate, and the filtrate concentrated to a cream solid. Column chromatography on silica, eluting with ethyl acetate/petrol (gradient elution, 20% - 80%), followed by recrystallisation from ethyl acetate gave the product as a pink crystalline solid (0.176g, 88%) with mp 147-148°C; (Found: C, 71.65; H, 5.58 N, 6.95. $C_{24}H_{22}N_2O_4$ requires: C, 71.63; H, 5.51; N, 6.96%); δH [$^2H_6$]-DMSO 8.65 (1H, s, 2-H), 7.29-7.52 (9H, m, 5-H, 8-H, 2'-H, 6'-H. 5 x PhH), 7.05 (2H, d, J 9, 3'-H. 5'-H), 5.58 (2H, s, QuinOCH_2), 5.13 (2H, s, $PhCH_2O$)3.95 and 3.89 (2 x 3H, 2 x s, 2 x CH_3O); m/z (%) 402 (68, M^+), 91 (100); ν_{max} (KBr disc)/cm^{-1} 1508, 1425, 1242, 1219.

Example 20

6,7-Dimethoxy-4-(4-phenoxybenzylamino)quinazoline

Lithium aluminium hydride (0.080g, 2.10 mmol) was added portionwise to dry ether (25 ml) with stirring under a nitrogen atmosphere. The grey suspension was cooled using an ice-water bath and 4-phenoxybenzonitrile (Apin) (0.20g, 1.02 mmol) was added. Stirring was continued overnight, with the mixture being allowed to warm to room temperature. TLC indicated that the reduction had not occurred, so the mixture was heated to reflux for 2 hours, and then allowed to cool. The mixture was diluted with ether, and allowed to settle. A yellow solution was decanted and carefully treated with water to give a yellow solid, which was collected by filtration. This was washed with hot methanol to leave 4-phenoxybenzylamine as an off-white solid (0.175g, 86%), which was not fully characterised due to instability; m/z (%) 199 (82, M-1$^+$), 183 (92), 77 (100). The reaction was repeated to obtain further product for use in the following step.

4-Chloro-6,7-dimethoxyquinazoline (0.200g, 0.89 mmol) and 4-phenoxybenzylamine (0.200g, 1.01 mmol) (added batchwise) were reacted in methanol (30 ml) for 6.5 hours according to Procedure A, under a nitrogen

atmosphere. The reaction mixture was concentrated to give a yellow oil, which was treated with triethylamine and partioned between water and ethyl acetate. The ethyl acetate extract was dried ($MgSO_4$) and concentrated to a pale yellow solid. Column chromatography on silica, eluting with methanol/chloroform (5%), gave the free base of the product as a pale yellow solid (0.070g). This was dissolved in acetone and treated with ethereal HCl solution to give the desired hydrochloride salt as a cream solid (0.070g, 18%) mp 250-252°C; (Found: C, 64.51; H, 5.24 N, 9.72. $C_{23}H_{21}N_3O_3.HCl.\ 0.2H_2O$ requires: C, 64.62; H, 5.28; N, 9.72%); δH [$^2H_6$]-DMSO 10.59 (1H, br t, J 5.5, NH), 8.78 (1H, s, 2-H), 8.16 (1H, s, 8-H), 7.45 (2H, d, J 9, 2'-H, 6'-H), 7.38 (2H, t, J 9, 3"-H, 5"-H), 7.32 (1H, s, 5-H), 7.12 (1H, t, J 8, 4"-H), 6.98 (4H, d, J 9, 3'-H, 5'-H, 2"-H, 6"-H), 4.91 (2H, d, J 7, QuinNHCH2), 3.99 (6H, s, 2 x CH_3O); m/z (%) 387 (100); ν_{max} (KBr disc)/cm^{-1} 1634, 1591, 1578, 1508, 1489, 1244.

Example 21

6,7-Dimethoxy-4-(3-phenoxyanilino)quinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.090 g; 0.40 mmol) and 3-phenoxyaniline (0.074 g; 0.40 mmol) were reacted in 2-propanol (3 ml) for 65 minutes according to Procedure B. The product was thus obtained as pale cream prisms (0.151 g, 92%) with mp 253-255°C; (Found C, 63.99; H, 4.88; N, 10.08; $C_{22}H_{19}N_3O_3.HCl.0.25H_2O$ requires C, 63.77; H, 4.95; N, 10.14); tlc (ethyl acetate) Rf 0.27; δH [$^2H_6$]-DMSO 11.26 (1H, br s, NH), 8.80 (1H, s, 2-H), 8.30 (1H, s, 8-H), 7.31-7.61 (7H, m, 5-H, 2'-H, 5'-H, 6'-H, 3"-H, 4"-H, 5"-H), 7.17 (1H, t, J 7, 4"-H), 7.09 (2H, d, J 9, 2"-H, 6"-H), 4.04 and 3.98 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 374 (100, M+1$^+$).

Example 22

4-(Phenoxyanilino)quinazoline hydrochloride

4-Chloroquinazoline (0.10 g, 0.61 mmol) and 4-phenoxyaniline (0.14 g, 0.73 mmol) were reacted in 2-propanol (15 ml) for 15 minutes according to Procedure B. The pale cream yellow solid thus obtained was 4-(phenoxyanilino)quinazoline hydrochloride (0.18 g, 84%), mp 275-277 °C; (Found: C, 68.26; H, 4.56; N, 11.84. $C_{20}H_{15}N_3O.HCl.0.1H_2O$ requires: C, 68.32; H, 4.64; N, 11.95%); δH [$^2H_6$]-DMSO 11.75 (1H, br s, NH), 9.01 (1H, d, J 9, 8-H), 8.95 (1H, s, 2-H), 8.19 (1H, t, J 9, 6-H), 8.08 (1H, d, J 9, 5-H), 7.93 (1H, t, J 9, 7-H), 7.85 (2H, d, J 9, 2'-H, 6'-H), 7.50 (2H, t, J 9, 3"-H, 5"-H), 7.26 (1H, t, J 9, 4"-H), 7.21 (2H, d, J 9, 3'-H, 5'-H), 7.15 (2H, d, J 9, 2"-H, 6"-H); m/z (%) 314 (100, M+1$^+$), 248 (100); ν_{max} (KBr disc)/cm^{-1} 1632, 1614, 1566, 1506, 1489, 1435, 1239, 1219.

Example 23

6,7-Dimethoxy-4-(4-phenoxyanilino)quinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.150g, 0.668 mmol) and 4-phenoxyaniline (0.185g, 0.675 mmol) were reacted in 2-propanol (4 ml) for 3 hours according to Procedure B. The yellow crystalline solid thus obtained was dried in vacuo at 60°C to give the product with mp 229-235°C (decomp); (Found: C, 61.84; H, 5.02 N, 9.73. $C_{22}H_{19}N_3O_3.HCl.H_2O$ requires: C, 61.75; H, 5.18; N, 9.82%); δH [$^2H_6$]-DMSO 11.37 (1H, br s, NH), 8.79 (1H, s, 2-H), 8.32 (1H, s, 8-H), 7.71 (2H, d, J 9, 2'-H, 6'-H), 7.44 (2H, d, J 8.5, 3"-H, 5"-H), 7.39 (1H, s, 5-H), 7.03-7.20 (5H, m, 3'-H, 5'-H, 2"-H, 4"-H, 6"-H), 4.01 and 3.99 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 373 (95, M^+), 372 (100); ν_{max} (KBr disc)/cm^{-1} 1633, 1570, 1514, 1504, 1437, 1228.

Example 24

4-(3-Benzyloxyanilino)quinazoline hydrochloride

4-Chloroquinazoline (0.100g, 0.608 mmol) and 3-benzyloxyaniline (0.120g, 0.602 mmol) were reacted in 2-propanol (4 ml) for 2 hours according to Procedure B. The yellow solid thus obtained was dried at 60°C to give the product (0.183g, 84%) with mp 205-207°C; (Found: C, 69.24; H, 5.01 N, 11.44. $C_{21}H_{17}N_3O.HCl$ requires: C, 69.32; H, 4.99; N, 11.55%); δH [$^2H_6$]-DMSO 11.63 (1H, br s, NH), 8.89-8.99 (2H, m, 2-H, 8-H), 8.14 (1H, t, J 8, 7-H), 8.00 (1H, d, J 8.5, 5-H), 7.89 (1H, t, J 8, 6-H), 7.30-7.54 (8H, m, 2'-H, 5'-H, 6'-H, 5 x PhH), 7.01 (1H, dt, J 9, 2, 4'-H), 5.19 (2H, s, CH_2); m/z (%) 328 (100, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1632, 1562, 1373.

Example 25

4-(4-Benzyloxyanilino)quinazoline hydrochloride

4-Chloroquinazoline (0.500g, 3.00 mmol) and 4-benzyloxyaniline (0.600g, 3.0 mmol) were reacted in 2-propanol (10 ml) for 1 hour according to Procedure A. The yellow solid thus obtained was the product (0.850g, 75%). A portion was recrystallised from hot 2-propanol to give a yellow crystalline solid with mp 200-203°C; (Found: C, 66.32; H, 4.94 N, 10.77. $C_{21}H_{17}N_3O.HCl.0.9H_2O$ requires: C, 66.36; H, 5.25; N, 11.06%); δH [$^2H_6$]-DMSO 11.59 (1H, br s, NH), 8.80-8.90 (2H, m, 2-H, 8-H), 8.12 (1H, t, J 8, 7-H), 7.82-7.99 (2H, m, 5-H, 6-H), 7.66 (2H, d, J 9, 2'-H, 6'-H), 7.30-7.55 (5H, m, 5 x PhH), 7.16 (2H, d, J 9, 3'-H, 5'-H), 5.19 (2H, s, CH_2); m/z (%) 328 (100, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1632, 1612, 1564, 1510, 1375.

Example 26

4-(4-Benzyloxyanilino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.710g, 3.16 mmol) and 4-benzyloxyaniline (1.10g, 5.52 mmol) were reacted in 2-propanol (25 ml) for 15 minutes according to Procedure B. The pale yellow crystalline solid thus obtained was dried in vacuo at 60oC to give the product (1.32g, 97%) with mp 253-255oC (decomp); (Found: C, 64.10; H, 5.21 N, 9.53. $C_{23}H_{21}N_3O_3.HCl.0.4H_2O$ requires: C, 64.08; H, 5.33; N, 9.75%); δH [$^2H_6$]-DMSO 11.43 (1H, br s, NH), 8.79 (1H, s, 2-H), 8.41 (1H, s, 8-H), 7.68 (2H, d, J 9, 2'-H, 6'-H), 7.38-7.58 (6H, m, 5-H, 5 x PhH), 7.19 (2H, d, J 9, 3'-H, 5'-H), 5.23 (2H, s, $PhCH_2$), 4.09 and 4.07 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 387 (85, M^+), 296 (100), 91 (100); ν_{max} (KBr disc)/cm^{-1} 1632, 1572, 1512, 1435, 1234.

Example 27

4-(4-Benzyloxyanilino)-6,7-dimethylquinazoline hydrochloride

6,7-Dimethyl-4-chloroquinazoline (0.200g, 1.04 mmol) and 4-benzyloxyaniline (0.200g, 1.00 mmol) were dissolved in 2-propanol (5 ml) for 5 min according to Procedure B. The yellow crystalline solid thus obtained was dried at 60oC to give the product (0.355g, 89%) ; (Found: C, 68.91; H, 5.51 N, 10.23. $C_{23}H_{21}N_3O.HCl.0.5H_2O$ requires: C, 68.91; H, 5.78; N, 10.48%); δH [$^2H_6$]-DMSO 11.56 (1H, br s, NH), 8.80 and 8.77 (2 x 1H, 2 x s, 2-H and 8-H), 7.74 (1H, s, 5-H), 7.68 (2H, d, J 10, 2'-H, 6'-H), 7.30-7.51 (5H, m, 5 x PhH), 7.12 (2H, d, J, 10, 3'-H, 5'-H), 5.18 (2H, s, $PhCH_2$), 2.50 and 2.49 (2 x 3H, 2 x s, 2 x CH_3); m/z (%) 356 (100, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1616, 1568, 1510, 1439, 1373, 1244.

Example 28

6,7-Dimethyl-4-(4-phenoxyanilino)quinazoline hydrochloride

4-Chloro-6,7-dimethylquinazoline (0.150g, 0.78mmol) and 4-phenoxyaniline (0.150g, 0.81mmol) were reacted in 2-propanol (6ml) according to Procedure B. The product was obtained as a yellow solid (0.240g, 81%), with mp 231-232°C; (Found: C, 69.18; H, 5.20; N, 11.04. $C_{22}H_{19}N_3O.HCl$.$0.2H_2O$ requires C, 69.27; H, 5.39; N, 11.04%); δH [$^2H_6$] -DMSO 11.52 (1H, b, NH), 8.85 (1H, s, 2-H), 8.77 (1H, s, 5-H), 7.74 (3H, m, 8-H, 2'-H, 6'-H), 7.40 (2H, t, 2xPh-H), 7.23-7.02 (5H, m, 3'-H, 5'-H, 3xPh-H); m/z 342 ($M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1639, 1616.

Example 29

4-(4-Benzyloxyanilino)-5-methoxyquinazoline hydrochloride

4-Chloro-5-methoxyquinazoline (0.200g, 1.03 mmol) and 4-benzyloxyaniline (0.220g, 1.10 mmol) were reacted in 2-propanol (6 ml) for 15 mins according to Procedure B. The product was thus obtained as a yellow crystalline solid (0.350g, 83%) with mp 161-165°C; (Found: C, 64.45; H, 5.23 N, 10.25. $C_{22}H_{19}N_3O_2.HCl.0.9H_2O$ requires: C, 64.43; H, 5.36; N, 10.25%); δH [$^2H_6$]-DMSO 10.89 (1H, br s, NH), 8.74 (1H, s, 2-H), 8.01 (1H, s, 8-H), 7.30-7.60 (9H, m, 6-H, 7-H, 2'-H, 6'-H, 5 x PhH), 7.12 (2H, d, J 9, 3'-H, 5'-H), 5.19 (2H, s, CH_2), 4.13 (3H, s, OCH_3); m/z (%) 357 (18, M^+), 266 (100); ν_{max} (KBr disc)/cm^{-1} 1626, 1506.

Example 30

4-(4-Benzyloxyanilino)-6-methoxyquinazoline hydrochloride

4-Chloro-6-methoxyquinazoline (0.100g, 0.514 mmol) and 4-benzyloxyaniline (0.100g, 0.502 mmol) were reacted in 2-propanol (5 ml) for 15 mins according to Procedure B. The product was thus obtained as a yellow solid (0.197g, 99%) with mp 238-241°C; (Found: C, 66.93; H, 5.05 N, 10.60. $C_{22}H_{19}N_3O_2.HCl$ requires: C, 67.09; H, 5.12; N, 10.67%); δH [$^2H_6$]-DMSO 11.56 (1H, br s, NH), 8.75 (1H, s, 2-H), 8.39 (1H, s, 5-H), 7.94 (1H, d, J 9, 8-H), 7.71 (1H, d, J 9, 7-H), 7.68 (2H, d, J 9, 2'-H, 6'-H), 7.30-7.52 (5H, m, 5 x PhH), 7.14 (2H, d, J 9, 3'-H, 5'-H), 5.19 (2H, s, CH_2), 4.01 (3H, s, OCH_3); m/z (%) 357 (26, M^+), 266 (100); ν_{max} (KBr disc)/cm^{-1} 1560.

Example 31

6-Acetoxy-4-(4-benzyloxyanilino)quinazoline hydrochloride

6-Acetoxy-4-chloroquinazoline (0.600g, 2.7mmol) and 4-benzyloxyaniline (0.450g, 2.3mmol) were reacted in 2-propanol (25ml) according to Procedure B for 20 minutes, to give the product as a yellow solid (0.800g, 84%), with mp 206-209°C; (Found: C, 62.99; H, 5.06; N, 9.25. $C_{23}H_{19}N_3O_3.HCl.0.9H_2O$ requires C, 63.04; H, 5.01; N, 9.58%); δH [$^2H_6$] -DMSO 11.54 (1H, b, NH), 8.88 (1H, s, 2-H), 8.76 (1H, s, 5-H), 8.08 (1H, d, 8-H), 8.76 (1H, d, 7-H), 7.67 (2H, d, 2'-H, 6'-H), 7.53-7.30 (5H, m, 5xPh-H), 7.11 (2H, d, 3'-H, 5'-H), 5.18 (2H, s, CH_2), 2.38 (3H, s, CH_3).

6-Acetoxy-4-(4-benzyloxyanilino)quinazoline hydrochloride (0.300g) was partitioned between ethyl acetate/triethylamine and water. The organic layer was separated, dried ($MgSO_4$) and concentrated under vacuum to give 6-acetoxy-4-(4-benzyloxyanilino)quinazoline as the free base (0.220g, 80%), which was used without further characterisation.

Example 32

4-(4-Benzyloxyanilino)-6-hydroxyquinazoline

To a solution of 6-acetoxy-4-(4-benzyloxyanilino)quinazoline (0.025g, 0.064mmol) in methanol (5ml) was added aqueous sodium hydroxide solution (1M, 3 drops), and the mixture was stirred at ambient temperature for 30 minutes. The solvent was removed under vacuum and the residue washed with water and dried at 60°C to give the product; δH [$^2H_6$] -DMSO 7.79 (1H, s, 2-H), 7.59 (2H, d, 2'-H, 6'-H), 7.50-7.29 (5H, m, 5xPh-H), 7.03 (1H, d, 8-H), 6.88 (2H. d, 3'-H, 5'-H), 6.78 (1H, s, 5-H), 6.60 (1H, d, 7-H), 5.07 (2H, s, CH_2).

Example 33

4-(4-Benzyloxyanilino)-7-methoxyquinazoline hydrochloride

4-Chloro-7-methoxyquinazoline (0.040g, 0.206 mmol) and 4-benzyloxyaniline (0.050g, 0.251 mmol) were reacted in 2-propanol (3 ml) for 2 hours according to Procedure B. The product was thus obtained as a yellow solid (0.070g, 86%) with mp 211-213°C; (Found: C, 66.94; H, 5.15 N, 10.68. $C_{22}H_{19}N_3O_2.HCl$ requires: C, 67.09; H, 5.12; N, 10.67%); δH [$^2H_6$]-DMSO 11.45 (1H, br s, NH), 8.84 (1H, br s, 8-H), 8.78 (1H, s, 2-H), 7.61 (2H, d, J 9, 2'-H, 6'-H), 7.30-7.49 (7H, m, 5-H, 6-H, 5 x PhH), 7.11 (2H, d, J 9, 3'-H, 5'-H), 5.14 (2H, s, CH_2), 3.98 (3H, s, OCH_3); m/z (%) 358 (26, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1633, 1510.

Following a repeat of this reaction, a sample of the hydrochloride salt (0.60g, 1.52 mmol) was treated with aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and concentrated in vacuo to give the free base (0.50g, 92%), which was used without further characterisation.

Example 34

4-(4-Benzyloxyanilino)-7-hydroxyquinazoline

4-(4-Benzyloxyanilino)-7-methoxyquinazoline (0.20mg, 0.56mmol) and sodium ethanethiolate (0.440g, 5.2mmol) were reacted in DMF (10ml) at 140°C for 4 hours. The DMF was removed under vacuum and the residue columned on silica gel eluting with 1:1 ethyl acetate/60-80 petrol. The concentrated product fractions were re-chromatographed on silica eluting with 9:1 chloroform/methanol. The solvent was removed under vacuum and the residue recrystallised from ethanol to give the product as a yellow solid (0.070g, 36%), with mp 275-277°C; (Found: C, 66.32; H, 4.83; N, 10.96. $C_{21}H_{17}N_3O_2.2H_2O$ requires C, 66.30; H, 5.03; N, 11.05%); δH [$^2H_6$] - DMSO 11.61 (1H, b, NH), 11.24 (1H, b, OH), 8.71(1H, s, 2-H), 8.67 (1H, d, 5-H), 7.58

(2H, d, 2'-H, 6'-H), 7.52-7.25 (7H, m, 6-H, 8-H, 5xPh-H), 7.10 (2H, d, 3'-H, 5'-H), 5.18 (2H, s, CH_2); m/z 344 (M^+); ν_{max} (KBr disc)/cm^{-1} 3007, 1632.

Example 35

7-Acetoxy-4-(4-benzyloxyanilino)quinazoline hydrochloride

7-Acetoxy-4-chloroquinazoline (0.100g, 0.45mmol) and 4-benzyloxyaniline (0.080g, 0.40mmol) were reacted in 2-propanol (25ml) according to Procedure B for 10 minutes, to give the product as a yellow solid (0.100g, 59%), with mp 212-215°C; (Found: C, 65.11; H, 4.68; N, 9.89. $C_{23}H_{19}N_3O_3.HCl.0.1H_2O$ requires C, 65.20; H, 4.81; N, 9.92%); δH [$^2H_6$] -DMSO 11.38 (1H, b, NH), 8.87 (1H, d, 5-H), 8.80 (1H, s, 2-H), 7.21 (1H, s, 8-H), 7.69-7.59 (3H, m, 6-H, 2'-H, 6'-H), 7.53-7.30 (5H, m, 5xPh-H), 7.13 (2H, d, 3'-H, 5'-H), 5.16 (2H, s, CH_2), 2.38 (3H, s, CH_3); m/z 385 (M^+); ν_{max} (KBr disc)/cm^{-1} 1769, 1634, 1620.

Example 36

4-(4-Benzyloxyanilino)-5,6-dimethoxyquinazoline hydrochloride

4-Chloro-5,6-dimethoxyquinazoline (0.200g, 0.77mmol) and 4-benzyloxyaniline (0.220g, 1.1mmol) were reacted in 2-propanol (6ml) at reflux for 10 minutes. The 2-propanol was removed under vacuum, the remaining yellow solid was washed with acetone, and then partitioned between ethyl acetate/triethylamine and water. The organic phase was separated and washed with water, dried ($MgSO_4$), and the solvent removed under vacuum. Column chromatography on silica gel eluting with ethyl acetate gave the free base of the desired product, which was acidified with ethereal HCl. The precipitate was collected by filtration to give the product as a yellow solid (0.210g , 70%), which decomposed above 120°C; (Found: C, 64.13; H, 5.09; N, 9.66. $C_{23}H_{21}N_3O_3.HCl.0.4H_2O$ requires C, 64.08; H, 5.33; N, 9.75%); δH [$^2H_6$] -DMSO 10.93 (1H, b, NH), 8.70 (1H, s, 2-H), 7.96 (1H, d, 8-H), 7.75 (1H, d, 7-H), 7.64 (2H, d, 2'-H, 6' -H), 7.55-7.30 (5H, m, 5xPh-H), 7.10 (2H, d, 3'-H, 5'-H), 5.15 (2H, s, CH_2), 4.15 (3H, s, OCH_3), 4.00 (3H, s, OCH_3); m/z 387 (M^+); ν_{max} (KBr disc)/cm^{-1} 1632, 1610.

Example 37

5,6-Dimethoxy-4-(4-phenoxyanilino)quinazoline hydrochloride

4-Chloro-5,6-dimethoxyquinazoline (0.150g, 0.51mmol) and 4-phenoxyaniline (0.200g, 1.0mmol) were reacted in 2-propanol (10ml) at reflux for 10 minutes. The 2-propanol was removed under vacuum, the remaining yellow solid was washed with acetone, then partitioned between ethyl acetate/triethylamine and water. The organic phase was

separated and washed with water, dried ($MgSO_4$), and the solvent removed under vacuum. Column chromatography on silica gel eluting with ethyl acetate gave the free base of the desired product, which was acidified with ethereal HCl. The precipitate was collected by filtration to give the product as a yellow solid (0.110g , 58%), which decomposed above 100°C; (Found: C, 63.74; H, 4.83; N, 9.95. $C_{22}H_{19}N_3O_3.HCl.0.25H_2O$ requires C, 63.77; H,4.99; N, 10.14%); δH [$^2H_6$] -DMSO 10.95 (1H, b, NH), 8.75 (1H, s, 2-H), 7.97 (1H, d, 8-H), 7.73 (3H, m, 7-H, 2'-H, 6'-H), 7.40 (2H, t, 2xPh-H), 7.25-7.00 (3H, m, 3xPh-H), 7.10 (2H, d, 3'-H, 5'-H), 4.15 (3H, s, OCH_3), 4.05 (3H, s, OCH_3); m/z 373 (M^+); ν_{max} (KBr disc)/cm^{-1} 1624, 1607.

Example 38

4-(4-Benzyloxyanilino)-6-fluoroquinazoline hydrochloride

4-Chloro-6-fluoroquinazoline (0.180g, 1.0mmol) and 4-benzyloxyaniline (0.180g, 0.9mmol) were reacted in 2-propanol (9ml) according to Procedure B. The product was obtained as a yellow solid (0.300g, 87%); with mp 192-195°C; (Found: C, 65.42; H, 4.34; N, 10.90. $C_{21}H_{16}FN_3O.HCl$.$0.2H_2O$ requires C, 65.44; H, 4.55; N, 10.90%); δH [$^2H_6$] -DMSO 11.41 (1H, b, NH), 8.86 (1H, s, 2-H), 8.80 (1H, d, 5-H), 8.08-7.96 (2H, m, 7-H, 8-H), 7.66 (2H, d, 2'-H, 6'-H), 7.53-7.32 (5H, m, 5xPh-H), 7.15 (2H, d, 3'-H, 5'-H), 5.16 (2H, s, CH_2); m/z 345 (M^+); ν_{max} (KBr disc)/cm^{-1} 1639, 1616.

Example 39

6-Fluoro-4-(4-phenoxyanilino)quinazoline hydrochloride

4-Chloro-6-fluoroquinazoline (0.175g, 0.96mmol) and 4-phenoxyaniline (0.175g, 0.94mmol) were reacted in 2-propanol (10ml) according to Procedure B. The product was obtained as a yellow solid (0.240g, 69%), which decomposed above 200°C; (Found: C, 65.20; H, 4.07; N, 11.30. $C_{20}H_{14}FN_3O.HCl$ requires C, 65.31; H, 4.11; N, 11.43%); δH [$^2H_6$] -DMSO 11.72 (1H, b, NH), 8.95 (1H, d, 5-H), 8.87 (1H, s, 2-H), 8.14-7.96 (2H, m, 7-H, 8-H), 7.78 (2H, d, 2'-H, 6'-H), 7.42 (2H, t, 2xPh-H), 7.22-7.03 (5H, m, 3'-H, 5'-H, 3xPh-H); m/z 331 (M^+); ν_{max} (KBr disc)/cm^{-1} 1614.

Example 40

4-(4-Benzyloxyanilino)-7-fluoroquinazoline hydrochloride

4-Chloro-7-fluoroquinazoline (0.500g, 2.7mmol) and 4-benzyloxyaniline (0.520g, 2.6mmol) were reacted in 2-propanol (30ml) for 10 minutes according to Procedure B. The product was obtained as a yellow solid (0.350g, 33%), which decomposes above 170°C; (Found: C, 66.18; H, 4.50; N, 11.25. $C_{21}H_{16}FN_3O.HCl$ requires C, 66.06; H, 4.49; N, 11.01%); δH [$^2H_6$] -DMSO 11.39 (1H, b, NH), 8.90 (1H, m, 5-H), 8.80 (1H, s,

2-H), 7.75 (1H, m, 6-H), 7.70 (1H, m, 8-H), 7.60 (2H, d, 2'-H, 6'-H), 7.53-7.32 (5H, m, 5xPh-H), 7.12 (2H, d, 3'-H, 5'-H), 5.14 (2H, s, CH_2); m/z 345 (M^+); ν_{max} (KBr disc)/cm^{-1} 1624, 1605.

Example 41

7-Fluoro-4-(4-phenoxyanilino)quinazoline hydrochloride

4-Chloro-7-fluoroquinazoline (0.230g, 1.26mmol) and 4-phenoxyaniline (0.230g, 1.24mmol) were reacted in 2-propanol (20ml) for 20 minutes according to Procedure B. The product was obtained as a yellow solid (90mg, 19%), with mp 209-211°C; (Found: C, 65.10; H, 4.12; N, 11.55. $C_{20}H_{14}FN_3O.HCl$ requires C, 65.31; H, 4.11; N, 11.43%); δH [$^2H_6$] -DMSO 11.32 (1H, b, NH), 8.90 (1H, m, 5-H), 8.83 (1H, s, 2-H), 7.80-7.65 (4H, m, 6-H, 8-H, 2'-H, 6'-H), 7.42 (2H, t, 2xPh-H), 7.21-7.02 (5H, m, 3'-H, 5'-H, 3xPh-H); m/z 331 (M^+); ν_{max} (KBr disc)/cm^{-1} 1626.

Example 42

4-(4-Benzyloxyanilino)-7-chloroquinazoline hydrochloride

4,7-Dichloroquinazoline (0.300g, 1.51 mmol) and 4-benzyloxyaniline (0.300g, 1.51 mmol) were reacted in 2-propanol (5 ml) for 10 min according to Procedure B. The product was thus obtained as a yellow solid (0.566g, 93%) with mp 230-233°C; (Found: C, 62.53; H, 4.25 N, 10.43. $C_{21}H_{17}ClN_3O.HCl.0.3H_2O$ requires: C, 62.48; H, 4.39; N, 10.41%); δH [$^2H_6$]-DMSO 11.71 (1H, br s, NH), 8.88 (1H, d, J 9, 5-H), 8.84 (1H, s, 2-H), 8.04 (1H, s, 8-H), 7.89 (1H, d, J 9, 6-H), 7.64 (2H, d, J 9, 2'-H, 6'-H), 7.30-7.51 (5H, m, 5 x PhH), 7.13 (2H, d, J 9, 3'-H, 5'-H), 5.18 (2H, s, CH_2); m/z (%) 361 (56, M^+), 270 (100); ν_{max} (KBr disc)/cm^{-1} 1632, 1614, 1566, 1508, 1373, 1248.

Example 43

4-(4-Benzyloxyanilino)-5-chloroquinazoline hydrochloride

4,5-Dichloroquinazoline (0.250g, 1.26mmol) and 4-benzyloxyaniline (0.250g, 1.25mmol) were reacted in 2-propanol (12ml) according to Procedure B. The product was obtained as a yellow solid (0.250g, 50%), with mp 170-173°C; (Found: C, 62.90; H, 4.20; N, 10.40. $C_{21}H_{16}ClN_3O.HCl.0.1H_2O$ requires C, 63.04; H, 4.33; N, 10.50%). δH [$^2H_6$] -DMSO 10.53 (1H, b, NH), 8.78 (1H, s, 2-H), 7.98 (1H, t, 7-H), 7.95-7.86 (2H, m, 6-H, 8-H), 7.60 (2H, d, 2'-H, 6' -H), 7.50-7.30 (5H, m, 5xPh-H), 7.11 (2H, d, 3'-H, 5'-H), 5.19 (2H, s, CH_2); m/z 361/363 (M^+); ν_{max} (KBr disc)/cm^{-1} 1626, 1605.

Example 44

5-Chloro-4-(4-phenoxyanilino)quinazoline hydrochloride

4,5-Dichloroquinazoline (0.200g, 1.0mmol) and 4-phenoxyaniline (0.200g, 1.1mmol) were reacted in 2-propanol (6ml) for 15 minutes according to Procedure B. The product was obtained as a yellow solid (0.144g, 37%), which decomposesd above 140°C; (Found: C, 61.40; H, 3.80; N, 10.66. $C_{20}H_{14}N_3O.HCl.0.4H_2O$ requires C, 61.36; H. 4.07; N, 10.73%). δH [$^2H_6$] -DMSO 10.68 (1H, b, NH), 8.84 (1H, s, 2-H), 8.01 (2H, m), 7.91 (1H, d), 7.70 (2H, d, 2'-H, 6' -H), 7.42 (2H, t, 2xPh-H), 7.22-7.05 (5H, m, 3'-H, 5'-H, 3xPh-H); m/z 346/348 ($M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1634, 1610.

Example 45

4-(4-Benzyloxyanilino)-6-chloroquinazoline hydrochloride

4,6-Dichloroquinazoline (0.200g, 1.0mmol) and 4-benzyloxyaniline (0.210g, 1.0mmol) were reacted in 2-propanol (5ml) according to Procedure B. The product was obtained as a yellow solid (0.360g, 90%); (Found: C, 62.05; H, 4.24; N, 10.08. $C_{21}H_{16}ClN_3O.HCl.0.5H_2O$ requires C, 61.93; H, 4.45; N, 10.32%); δH [$^2H_6$] -DMSO 11.60 (1H, b, NH), 9.11 (1H, s, 5-H), 8.85 (1H, s, 2-H), 8.10 (1H, d, 7-H), 8.01 (1H, d. 8-H), 7.68 (2H, d, 2'-H, 6'-H), 7.50-7.30 (5H, m, 5xPh-H), 7.14 (2H, d, 3'-H, 5'-H), 5.14 (2H, s, CH_2); m/z 361/363 (M^+).

Example 46

6-Chloro-4-(4-phenoxyanilino)quinazoline hydrochloride

4,6- Dichloroquinazoline (0.150g, 0.75mmol) and 4-phenoxyaniline (0.150g, 0.81mmol) were reacted in 2-propanol (5ml) for 2 minutes according to Procedure B. The product was obtained as a yellow solid (0.205g, 71%), with mp 214-216°C; (Found: C, 61.40: H, 3.81; N, 10.78. $C_{20}H_{14}ClN_3O.HCl.0.4H_2O$ requires C, 61.36; H, 4.07; N, 10.73%); δH [$^2H_6$] -DMSO 11.45 (1H, b, NH), 9.05 (1H, s, 5-H), 8.89 (1H, s, 2-H), 8.10 (1H, d, 7-H), 7.98 (1H, d, 8-H), 7.79 (2H, d, 2'-H, 6'-H), 7.45 (2H, t, 2xPh-H), 7.22-7.00 (5H, m, 3'-H, 5'-H, 3xPh-H); m/z 348/350 ($M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1632, 1612.

Example 47

4-(4-Benzyloxyanilino)-6,7-dichloroquinazoline hydrochloride

4,6,7- Trichloroquinazoline (0.070g, 0.30mmol) and 4-benzyloxyaniline (0.110g, 0.55mmol) were reacted in 2-propanol (5ml) at reflux for 5 minutes. The 2-propanol was removed under vacuum and the reaction triturated with acetone to give the product as yellow crystals (0.080g, 62%), with mp 237-238°C; (Found: C, 57.70; H, 3.55; N,

9.54. $C_{21}H_{15}Cl_2N_3O.HCl.0.25H_2O$ requires C, 57.68; H, 3.80; N, 9.61%); δH [$^2H_6$] -DMSO 11.08 (1H, b, NH), 9.10 (1H, s), 8.77 (1H, s), 8.10 (1H, s), 7.68 (2H, d, 2'-H, 6'-H), 7.50-7.30 (5H, m, 5xPh-H), 7.12 (2H, d, 3'-H, 5'-H), 5.19 (2H, s, CH_2); m/z 395/397/399 (M^+); ν_{max} (KBr disc)/cm^{-1} 1630, 1605.

Example 48

4-(4-Benzyloxyanilino)-6-bromoquinazoline hydrochloride

4-Chloro-6-bromoquinazoline (0.250g, 1.0mmol) and 4-benzyloxyaniline (0.250g, 1.3mmol.) were mixed in 2-propanol (6ml) and heated at reflux for 10 minutes. The solution was allowed to cool to room temperature and the 2-propanol removed under vacuum. The resulting solid was triturated with acetone to give the product as a yellow solid (0.390g , 88%); (Found: C, 56.38; H, 3.82; N, 9.24. $C_{21}H_{16}N_3O.HCl.0.25H_2O$ requires C, 56.39; H, 3.94; N, 9.40%); δH [$^2H_6$] -DMSO 11.60 (1H, b, NH), 9.21 (1H, s, 5-H), 8.86 (1H, s, 2-H), 8.20 (1H, d, 7-H), 7.90 (1H, d, 8-H) 7.65 (2H, d, 2'-H, 6'-H), 7.50-7.25 (5H, m, Ph-H), 7.10 (2H, d, 3'-H, 5'-H), 5.15 (2H, s, CH_2); m/z 405/407 (M^+).

Example 49

6-Bromo-4-(4-phenoxyanilino)quinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.150g, 0.62mmol) and 4-phenoxyaniline (0.150g, 0.81mmol) were reacted in 2-propanol (6ml) for 2 minutes according to Procedure B. The product was obtained as a yellow solid (0.130g, 49%); (Found: C, 54.85; H, 3.45; N, 9.58. $C_{20}H_{14}N_3O.HCl.0.5H_2O$ requires C, 54.88; H, 3.68; N, 9.60%); δH [$^2H_6$] -DMSO 11.59 (1H, b, NH), 9.21 (1H, s, 5-H), 8.88 (1H, s, 2-H), 8.20 (1H, d, 7-H), 7.92 (1H, d, 8-H) 7.72 (2H, d, 2'-H, 6'-H), 7.45 (2H, t, 2xPh-H), 7.22-7.00 (5H, m, 3'-H, 5'-H, 3xPh-H); m/z 392/394 (M^+); ν_{max} (KBr disc)/cm^{-1} 1630, 1610.

Example 50

4-(4-Benzyloxyanilino)-6-iodoquinazoline hydrochloride

4-Chloro-6-iodoquinazoline (0.360g, 1.24mmol) and 4-benzyloxyaniline (0.320g, 1.61mmol) were reacted in 2-propanol (10ml) for 2 minutes according to Procedure B. The product was obtained as a yellow solid (0.440g, 72%), with mp 204-207°C; (Found: C, 51.11; H, 3.52; N, 8.32. $C_{21}H_{16}IN_3O.HCl.0.2H_2O$ requires C, 51.13; H, 3.56; N, 8.52%); δH [$^2H_6$] -DMSO 11.51 (1H, b, NH), 9.27 (1H, s, 5-H), 8.86 (1H, s, 2-H), 8.34 (1H, d, 7-H), 7.75 (1H, d, 8-H), 7.64 (2H, d, 2'-H, 6'-H), 7.51-7.30 (5H, m, 5xPh-H), 7.12 (2H, d, 3'-H, 5'-H), 5.18 (2H, s, CH_2); m/z 453 (M^+); ν_{max} (KBr disc)/cm^{-1} 1632, 1603.

Example 51

6-Iodo-4-(4-phenoxyanilino)quinazoline hydrochloride

4-Chloro-6-iodoquinazoline (0.350g, 1.2mmol) and 4-phenoxyaniline (0.300g, 1.6mmol) were reacted in 2-propanol (15ml) according to Procedure B. The product was obtained as a yellow solid (0.370g, 65%), with mp 237-239°C; (Found: C, 50.23; H, 3.06; N, 8.78. $C_{20}H_{14}IN_3O.HCl$ requires C, 50.49; H, 3.18; N, 8.83%); δH [$^2H_6$] -DMSO 11.41 (1H, b, NH), 9.27 (1H, s, 5-H), 8.89 (1H, s, 2-H), 8.34 (1H, d, 7-H), 7.75 (3H, m, 8-H, 2'-H, 6'-H), 7.41 (2H, t, 2xPh-H), 7.22-7.04 (5H, m, 3'-H, 5'-H, 3xPh-H); m/z 349 (M^+); ν_{max} (KBr disc)/cm^{-1} 1624, 1605.

Example 52

4-(4-Benzyloxyanilino)-6-trifluoromethoxyquinazoline hydrochloride

4-Chloro-6-trifluoromethoxyquinazoline (0.360g, 1.45mmol) and 4-benzyloxyaniline (0.390g, 1.96mmol) were reacted in 2-propanol (4ml) according to Procedure B. The product was obtained as a yellow solid (0.500g, 77%), which decomposed above 180°C; (Found: C, 58.71; H, 3.76; N, 9.23. $C_{22}H_{16}F_3N_3O_2.HCl$ requires C, 59.00: H, 3.83; N, 9.38%); δH [$^2H_6$] -DMSO 11.40 (1H, b, NH), 8.87 (1H, s, 5-H), 8.83 (1H, s, 2-H), 8.05 (2H, s, 7-H, 8-H), 7.63 (2H, d, 2'-H, 6'-H), 7.51-7.30 (5H, m, 5xPh-H), 7.12 (2H, d, 3'-H, 5'-H), 5.15 (2H, s, CH_2); m/z 411 (M^+); ν_{max}(KBr disc)/cm^{-1} 1639, 1616.

Example 53

4-(4-Benzyloxyanilino)-7-(trifluoromethyl)quinazoline hydrochloride

4-Chloro-7-(trifluoromethyl)quinazoline (0.100g, 0.43mmol) and 4-benzyloxyaniline (0.090g, 0.45mmol) were reacted at reflux in 2-propanol (4ml) for 4 hours. The solvent was removed under vacuum and the residue washed with acetone. The solid was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and the solvent removed under vacuum. The resulting solid was dissolved in acetone and treated with ethereal HCl to precipitate the salt, which was collected by filtration to give the product as a yellow solid (0.035g, 19%), which decomposed above 270°C; (Found: C, 60.28; H, 3.79; N, 9.70. $C_{22}H_{16}F_3N_3O.HCl.0.4H_2O$ requires C, 60.18; H, 4.09; N, 9.57%); δH [$^2H_6$] -DMSO 11.02 (1H, b, NH), 8.93 (1H, d, 5-H), 8.81 (1H, s, 2-H), 8.17 (1H, s, 8-H), 8.07 (1H, d, 6-H), 7.65 (2H, d, 2'-H, 6'-H), 7.53-7.26 (5H, m, 5xPh-H), 7.13 (2H, d, 3'-H, 5'-H), 5.18 (2H, s, CH_2); m/z 395 (M^+); ν_{max} (KBr disc)/cm^{-1} 1616.

Example 54

4-(4-Benzyloxyanilino)-6-nitroquinazoline hydrochloride and free base

4-Chloro-6-nitroquinazoline (0.600g, 2.9mmol) and 4-benzyloxyaniline (0.600g, 3.0mmol) were reacted in 2-propanol (30ml) according to Procedure B, to give the product as a yellow solid (0.900g, 77%), with mp 222-223°C; (Found: C, 61.13; H, 4.11; N, 13.41. $C_{21}H_{16}N_4O_3.HCl.0.2H_2O$ requires C, 61.13; H, 4.25; N, 13.58%); δH [$^2H_6$] -DMSO 11.58 (1H, b, NH), 9.78 (1H, s, 5-H), 8.87 (1H, s, 2-H), 8.70 (1H, d, 7-H), 8.08 (1H, d, 8-H), 7.66 (2H, d, 2'-H, 6' -H), 7.52-7.30 (5H, m, 5xPh-H), 7.13 (2H, d, 3'-H, 5'-H), 5.18 (2H, s, CH_2); m/z 372 (M^+); ν_{max} (KBr disc)/cm^{-1} 1635, 1614.
A portion of this material (0.800g, 1.94mmol) was converted to the free base by partitioning between ethyl acetate/triethylamine and water. The organic phase was washed with water, dried ($MgSO_4$) and concentrated under vacuum to give the free base as a yellow solid (0.690g, 97%), which was used without further characterisation.

Example 55

6-Amino-4-(4-benzyloxyanilino)quinazoline

4-(4-Benzyloxyanilino)-6-nitroquinazoline (1g, 2.9mmol) and Raney Nickel (ex. Fluka, prewashed with methanol) were suspended in methanol (50ml). Hydrazine hydrate (11ml) was added dropwise and the reaction stirred at ambient temperature for 3 hours. The solvent was removed under vacuum and the reaction diluted with water. The precipitate was filtered off, washed with water, and dried at 60°C under vacuum to give the product as a beige solid (0.900g, 99%); (Found: C, 71.61; H, 5.43; N, 15.80. $C_{21}H_{18}N_4O.0.5H_2O$ requires C, 71.78; H, 5.45; N, 15.94%). δH [$^2H_6$] -DMSO 9.12 (1H, b, NH), 8.26 (1H, s, 2-H), 7.71 (2H, d, 2'-H, 6' -H), 7.53-7.30 (7H, m, 5-H, 8-H, 5xPh-H), 7.21 (1H, d, 7-H), 7.01 (2H, d, 3'-H, 5'-H), 5.43 (2H, b, NH_2), 5.12 (2H, s, CH_2); m/z 342 (M^+); ν_{max} (KBr disc)/cm^{-1} 3309, 3200, 1632, 1601.

Example 56

4-(4-Benzyloxyanilino)-6-ureidoquinazoline

6-Amino-4-(4-benzyloxyanilino)quinazoline (0.170g, 0.50mmol) was dissolved in ethyl acetate (40ml) and added dropwise to a solution of triphosgene (0.150g, 0.51mmol) in ethyl acetate (20ml). On completion of the addition, the reaction was stirred for 10 minutes then .880 ammonia (25ml) was added. The solvent was removed under vacuum, the residue washed with water and dried at 60°C under vacuum to give the product as a yellow solid (0.100g, 52%); δH [$^2H_6$] -DMSO 9.50 (1H, b, NH), 8.67 (1H, b, NH), 8.39 (1H, s, 2-H), 8.29 (1H, s, 5-H), 7.88 (1H, d, 7-H), 7.67 (3H, m, 6-H, 2'-H,

6' -H), 7.50-7.30 (5H, m, 5xPh-H), 7.03 (2H, d, 3'-H, 5'-H), 5.99 (2H, b, NH_2), 5.12 (2H, s, CH_2); m/z 386 ($M+1^+$); ν_{max} (KBr disc)/cm^{-1} 3470, 3309, 1657, 1634, 1607.

Example 57

6-Acetamido-4-(4-benzyloxyanilino)quinazoline

6-Amino-4-(4-benzyloxyanilino)quinazoline (0.200g, 0.58mmol) was reacted with acetic anhydride (0.06ml, 0.58mmol) in dimethylacetamide (2ml) for 80 hours. The solution was diluted with water and the precipitate collected by filtration, washed with water, and dried at 60°C to give the product as a beige solid (0.150g, 67%); with mp 225-228°C; (Found: C, 68.01; H, 5.55; N, 13.74. $C_{23}H_{20}N_4O_2$. $1.2H_2O$ requires C, 68.03; H, 5.56; N,13.80%); δH [$^2H_6$] -DMSO 10.14 (1H, b, NH), 9.58 (1H, b, NH), 8.59 (1H, s, 5-H), 8.41 (1H, s, 2-H), 7.80 (1H, d, 7-H), 7.70 (1H, d, 8-H), 7.64 (2H, d, 2'-H, 6' -H), 7.50-7.29 (5H, m, 5xPh-H), 7.03 (2H, d, 3'-H, 5'-H), 5.12 (2H, s, CH_2), 2.10 (3H, s, CH_3).

Example 58

6-Nitro-4-(4-phenoxyanilino)quinazoline hydrochloride

4-Chloro-6-nitroquinazoline (0.130g, 0.62mmol) and 4-phenoxyaniline (0.130g, 0.70mmol) were reacted in 2-propanol (3ml) according to procedure B, to give the product as an orange solid (0.200g, 82%), which decomposed above 200°C; (Found: C, 60.35; H, 3.79; N, 13.94. $C_{20}H_{14}N_4O_3$.HCl.$0.2H_2O$ requires C, 60.29; H,3.90; N, 14.06%); δH [$^2H_6$] -DMSO 11.78 (1H, b, NH), 9.85 (1H, s, 5-H), 8.91 (1H, s, 2-H), 8.72 (1H, d, 7-H), 8.15 (1H, d, 8-H), 7.78 (2H, d, 2'-H, 6'-H), 7.48 (2H, t, 2xPh-H), 7.30-7.00 (6H, m, 3'-H, 5'-H, 3xPh-H); m/z 359 ($M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1635, 1616.

This material was converted to the free base by partitioning between ethyl acetate/triethylamine and water. The organic phase was washed with water, dried ($MgSO_4$) and concentrated under vacuum to give the free base as a yellow solid, which was used without further charaterisation.

Example 59

6-Amino-4-(4-phenoxyanilino)quinazoline

6-Nitro-4-(4-phenoxyanilino)quinazoline (0.250g, 0.70mmol) and 10% palladium on carbon (0.025g) were suspended in ethanol (15ml). Ammonium formate (0.250g, 4.0mmol) was added and the reaction stirred at ambient temperature for 3 hours. The mixture was filtered through hyflo and the solvent removed under vacuum. Column chromatography on silica, eluting with ethyl acetate, gave the product as a yellow solid

(0.100g, 44%), with mp 187-191°C; (Found: C, 71.97; H, 4.82; N, 16.52. $C_{20}H_{16}N_4O.0.3H_2O$ requires C, 71.97; H,4.82; N, 16.79%); δH [$^2H_6$] -DMSO 9.70 (1H, b, NH), 8.83 (1H, s, 2-H), 7.38 (2H, d, 2'-H, 6'-H), 7.53 (1H, d, 8-H), 7.45-7.30 (3H, m, 5-H, 2xPh-H), 7.25 (1H, d, 7-H), 7.20-6.90 (5H, m, 3'-H, 5'-H, 3xPh-H), 5.50 (2H, b, NH_2); m/z 328 (M^+); ν_{max} (KBr disc)/cm^{-1} 3340, 3217, 1632.

Example 60

4-(4-Benzyloxyanilino)-7-nitroquinazoline hydrochloride

4-Chloro-7-nitroquinazoline (1.2g, 5.7mmol) and 4-benzyloxyaniline (1.2g, 6.0mmol) were reacted in 2-propanol (50ml) according to Procedure B, to give the product as an orange solid (2g, 86%), with mp 195-198°C; (Found: C, 60.55; H, 4.25; N, 13.61. $C_{21}H_{16}N_4O_3.HCl.0.4H_2O$ requires C, 60.62; H, 4.31; N, 13.47%). δH [$^2H_6$] -DMSO 11.42 (1H, b, NH), 9.02 (1H, d, 5-H), 8.87 (1H, s, 2-H), 8.11 (1H, s, 8-H), 8.48 (1H, d, 6-H), 7.68 (2H, d, 2'-H, 6' -H), 7.51-7.30 (5H, m, 5xPh-H), 7.11 (2H, d, 3'-H, 5'-H), 5.16 (2H, s, CH_2); m/z 372 (M^+); ν_{max} (KBr disc)/cm^{-1} 1626.

A portion of this material (1.8g, 4.33mmol) was converted to the free base by partitioning between ethyl acetate/triethylamine and water. The organic phase was washed with water, dried ($MgSO_4$) and concentrated under vacuum to give the free base as a yellow solid (1.5g, 93%), which was used without further purification.

Example 61

7-Amino-4-(4-benzyloxyanilino)quinazoline

4-(4-Benzyloxyanilino)-7-nitroquinazoline (0.100g, 0.27mmol) and Raney Nickel (ex. Fluka, prewashed with methanol) were suspended in methanol (10ml). Hydrazine hydrate (1ml) was added dropwise and the reaction stirred at ambient temperature for 10 minutes. The reaction was filtered and the solvent removed under vacuum. The solution was diluted with water and the precipitate collected by filtration, washed with water, and dried at 60°C under vacuum to give the product as a beige solid (0.060g, 65%), with mp 249-251°C; (Found: C, 72.28; H, 5.17; N, 15.96. $C_{21}H_{18}N_4O.0.4H_2O$ requires C, 72.14; H, 5.42; N, 16.03%). δH [$^2H_6$] -DMSO 9.15 (1H, b, NH), 8.26 (1H, s, 2-H), 8.11 (1H, d, 5-H), 7.65 (2H, d, 2'-H, 6' -H), 7.51-7.30 (5H, m, 5xPh-H), 7.00 (2H, d, 3'-H, 5'-H), 6.88 (1H, d, 6-H), 6.59 (1H, s, 8-H), 5.88 (2H, b, NH_2), 5.10 (2H, s, CH_2); m/z 342 (M^+); ν_{max} (KBr disc)/cm^{-1} 3488, 3365, 1630, 1614.

Example 62

4-(4-Benzyloxyanilino)-7-(3,3-dimethylureido)quinazoline

7-Amino-4-(4-benzyloxyanilino)quinazoline (0.170g, 0.50mmol) dissolved in a 1:1 mixture of acetone and ethyl acetate (40ml) was added dropwise to triphosgene (0.150g, 0.51mmol) dissolved in ethyl acetate (20ml). On completion of the addition, the reaction was stirred for 10 minutes, and then dimethylamine was bubbled through the reaction for 5 minutes. The solvent was removed under vacuum, and the residue partitioned between ethyl acetate and water. The organic phase was washed with water, dried ($MgSO_4$), and concentrated under vacuum. Trituration with ethyl acetate/petrol gave the product as a yellow solid (0.102g, 50%), which decomposed above 200°C; (Found: C, 69.93; H, 5.55; N, 16.81. $C_{24}H_{23}N_5O_2$ requires C, 69.72; H, 5.61; N, 16.94%). δH [$^2H_6$] -DMSO 9.42 (1H, b, NH), 8.67 (1H, b, NH), 8.42 (1H, s, 2-H), 8.33 (1H, d, 5-H), 7.90 (1H, s, 8-H), 7.75 (1H, d, 6-H), 7.69 (2H, d, 2'-H, 6' -H), 7.53-7.28 (5H, m, 5xPh-H), 7.03 (2H, d, 3'-H, 5'-H), 5.12 (2H, s, CH_2), 2.96 (6H, s. 2xCH_3); m/z 413 (M^+); ν_{max} (KBr disc)/cm^{-1} 3306, 1659, 1622, 1605.

Example 63

4-(4-Benzyloxyanilino)-7-ureidoquinazoline

7-Amino-4-(4-benzyloxyanilino)quinazoline (0.170g, 0.50mmol) dissolved in a 1:1 mixture of acetone and ethyl acetate (40ml) was added dropwise to triphosgene (0.150g, 0.51mmol) dissolved in ethyl acetate (20ml). On completion of the addition, the reaction was stirred for 10 minutes and then .880 ammonia (25ml) was added. The solvent was removed under vacuum, and the residue was washed with water and dried at 60°C under vacuum to give the product as a yellow solid (0.093g, 48%); which decomposed above 270°C; (Found: C, 66.23; H, 4.76; N, 17.75. $C_{22}H_{19}N_5O_2$. $0.4H_2O$ requires C, 66.48; H, 5.16; N, 17.62%); δH [$^2H_6$] -DMSO 9.44 (1H, b, NH), 8.96 (1H, b, NH), 8.49 (1H, s, 2-H), 8.32 (1H, d, 5-H), 7.85 (1H, s, 8-H), 7.69 (2H, d, 2'-H, 6' -H), 7.55 (1H, d, 6-H), 7.50-7.28 (5H, m, 5xPh-H), 7.02 (2H, d, 3'-H, 5'-H), 6.02 (2H, b, NH_2), 5.11 (2H, s, CH_2); m/z 386 ($M+1^+$); ν_{max} (KBr disc)/cm^{-1} 3329, 1713, 1635, 1605.

Example 64

7-Acetamido-4-(4-benzyloxyanilino)quinazoline

7-Amino-4-(4-benzyloxyanilino)quinazoline (0.200g, 0.58mmol) was reacted with acetic anhydride (0.06ml, 0.58mmol) in dimethylacetamide (2ml) for 80 hours. The reaction was diluted with acetone, and the precipitate was collected by filtration, washed with acetone and dried at 60°C to give the product as a cream solid (0.140g, 62%) which did not melt up to 300°C; (Found: C, 70.97; H, 5.25; N, 14.34. $C_{23}H_{20}N_4O_2$. $0.25H_2O$ requires C, 71.03; H, 5.31; N, 14.41%); δH [$^2H_6$] -DMSO 10.26 (1H, b, NH),

9.51 (1H, b, NH), 8.43 (1H, s, 2-H), 8.39 (1H, d, 5-H), 8.50 (1H, s, 8-H), 7.69 (3H, m, 6-H, 2'-H, 6' -H), 7.50-7.30 (5H, m, 5xPh-H), 7.03 (2H, d, 3'-H, 5'-H), 5.12 (2H, s, CH_2), 2.12 (3H, s, CH_3).

Example 65

7-Nitro-4-(4-phenoxyanilino)quinazoline

4-Chloro-7-nitroquinazoline (0.940g, 4.5mmol) and 4-phenoxyaniline (0.940g, 5.0mmol) were reacted in 2-propanol (30ml) according to Procedure B. The product was obtained as a bright yellow solid (1.5g, 84%), with mp 214-215°C; (Found: C, 60.82; H, 3.73; N, 13.86. $C_{20}H_{14}N_4O_3.HCl$ requires C, 60.84; H, 3.83; N, 14.19%); δH [$^2H_6$] -DMSO 11.45 (1H, b, NH), 9.10 (1H, d, 5-H), 8.92 (1H, s, 2-H), 8.67 (1H, s, 8-H), 8.46 (1H, d, 6-H), 7.29 (2H, d, 2'-H, 6'-H), 7.43 (2H, t, 2xPh-H), 7.20-7.00 (5H, m, 3'-H, 5'-H, 3xPh-H); m/z 358 (M^+); ν_{max} (KBr disc)/cm^{-1} 1626.

A portion of this material (1g, 2.53mmol) was converted to the free base by partitioning between ethyl acetate/triethylamine and water. The organic phase was washed with water, dried ($MgSO_4$) and concentrated under vacuum to give the free base as a yellow solid (0.870g, 96%), which was used without further characterisation..

Example 66

7-Amino-4-(4-phenoxyanilino)quinazoline

7-Nitro-4-(4-phenoxyanilino)quinazoline (0.100g, 0.28mmol) and Pd/C (10%, 0.010g) were stirred in 2-methoxyethanol (20ml) and hydrogenated at 1 Atm. for 42 hours. The mixture was filtered through hyflo, washing with excess ethanol. The solvent was removed from the combined filtrate and washings under vacuum. The resulting oil was crystallised from ethyl acetate/petrol to give the product as a white solid (0.070mg, 76%); (Found: C, 70.89; H, 5.00; N, 16.11. $C_{20}H_{16}N_4O.0.67H_2O$ requires C, 70.56; H, 5.13; N, 16.46%); δH [$^2H_6$] -DMSO 9.28 (1H, b, NH), 8.32 (1H, s, 2-H), 8.15 (1H, d, 5-H), 7.82 (2H, d, 2'-H, 6'-H), 7.39 (2H, t, 2xPh-H), 7.12 (1H, t, 1xPh-H), 7.17-6.97 (4H, m, 3'-H, 5'-H, 2xPh-H), 6.90 (1H, d, 6-H), 6.71 (1H, s, 8-H), 6.40 (2H, b, NH_2); m/z 328 (M^+); ν_{max} (KBr disc)/cm^{-1} 3336, 3213, 1630, 1616.

Example 67

4-(4-Benzyloxyanilino)-6-methylthioquinazoline hydrochloride

4-Chloro-6-methylthioquinazoline (0.300g, 1.4mmol) and 4-benzyloxyaniline (0.300g, 1.5mmol) were reacted in 2-propanol (6ml) according to Procedure B. The product was obtained as a yellow solid (0.535g, 93%), which decomposes above 190°C ; (Found: C, 64.17; H, 4.80; N, 9.90. $C_{22}H_{19}N_3OS.HCl.0.2H_2O$ requires C, 63.89; H, 4.97; N,

10.16%); δH [$^2H_6$] -DMSO 11.49 (1H, b, NH), 8.82 (1H, s, 2-H), 8.55 (1H, s, 5-H), 7.98 (1H, s, 7-H), 7.84 (1H, d, 8-H), 7.62 (2H, d, 2'-H, 6'-H), 7.50-7.30 (5H, m, 5xPh-H), 7.12 (2H, d, 3'-H, 5'-H), 5.15 (2H, s, CH_3); m/z 373 (M^+); ν_{max} (KBr disc)/cm^{-1} 1624, 1612.

Example 68

4-(4-Benzyloxyanilino)-6-methylsulphonylquinazoline and 4-(4-Benzyloxyanilino)-6-methylsulphinylquinazoline

4-(4-Benzyloxyanilino)-6-methylmercaptoquinazoline hydrochloride (0.331g, 0.80 mmol) was suspended in methanol (15 ml), and the mixture cooled to 0-5°C, by use of an ice-water bath. Water (15 ml) was added, followed by Oxone® ($2KHSO_5.KHSO_4.K_2SO_4$, 0.370g, 0.602 mmol, 1.2 mmol oxidant) added portionwise over 30 minutes. The mixture was stirred at 0-5°C for 7 hours, and then allowed to cool to room temperature overnight. TLC showed no remaining starting material and two potential products. The reaction mixture was partitioned between ethyl acetate and brine, and the aqueous was further extracted with ethyl acetate until no further yellow colour remained in the aqueous. The combined organic extracts were dried ($MgSO_4$) and concentrated to a yellow solid. The mixture was dissolved in hot THF , allowed to cool and treated with ethyl acetate. A yellow solid crystallised, which TLC indicated to be the sulphoxide. The remaining solution was concentrated and purified by column chromatography on silica, eluting with methanol/ethyl acetate (gradient elution, 0% - 25%). The initial product eluted was the sulphone, 4-(4-benzyloxyanilino)-6-methylsulphonylquinazoline (0.133g, 38%), which was obtained as a pale yellow solid; δH [$^2H_6$]-DMSO 10.23 (1H, s, N-H), 9.19 (1H, s, 5-H), 8.62 (1H, s, 2-H), 8.25 (1H, d, J 9, 7-H), 7.93 (1H, d, J 8.5, 8-H), 7.67 (2H, d, J 9, 2'-H, 6'-H), 7.48 (2H, d, 7-H, 2"-H, 6"-H), 7.41 (2H, d, J 7.5, 3"-H, 5"-H), 7.34 (1H, t, J 7, 4"-H), 7.07 (2H, d, J 9, 3'-H, 5'-H), 5.15 (2H, s, CH_2), 3.32 (3H, s, SO_2CH_3); m/z (%) 405 (30, M^+), 314 (100), 91 (62); ν_{max} (KBr disc)/cm^{-1} 1572, 1535, 1508, 1431.

With more polar eluant a more polar product was obtained. This was concentrated and combined with the material obtained previously by crystallisation (identical by TLC) to give the sulphoxide product as a yellow solid (0.191g, 56%); δH [$^2H_6$]-DMSO 10.01 (1H, s, N-H), 8.85 (1H, s, 5-H), 8.59 (1H, s, 2-H), 8.09 (1H, d, J 9, 7-H), 7.91 (1H, d, J 9, 8-H), 7.70 (2H, d, J 9, 2'-H, 6'-H), 7.48 (2H, d, 8-H, 2"-H, 6"-H), 7.42 (2H, d, J 8, 3"-H, 5"-H), 7.30-7.38 (1H, m, 4"-H), 7.06 (2H, d, J 9, 3'-H, 5'-H), 5.12 (2H, s, CH_2), 2.87 (3H, s, $SOCH_3$); m/z (%) 389 (27, M^+), 373 (29), 298 (48), 282 (100), 91 (61); ν_{max} (KBr disc)/cm^{-1} 1572, 1531, 1510, 1488, 1236.

Example 69

6-Methylthio-4-(4-phenoxyanilino)quinazoline hydrochloride

4-Chloro-6-methylthioquinazoline (0.150g, 0.7mmol) and 4-phenoxyaniline (0.150g, 0.8mmol) were reacted in 2-propanol (6ml) according to Procedure B. The product was obtained as a yellow solid (0.240g, 87%), which decomposes above 190°C; (Found: C, 63.49; H, 4.56; N, 10.63. $C_{21}H_{17}N_3OS.HCl$ requires C, 63.71; H, 4.58; N, 10.61%); δH [$^2H_6$] -DMSO 11.68 (1H, b, NH), 8.80 (1H, s, 2-H), 8.64 (1H, s, 5-H), 8.00 (1H, d, 7-H), 7.93 (1H, d, 8-H), 7.75 (2H, d, 2'-H, 6'-H), 7.46 (2H, t, 2xPh-H), 7.23-7.02 (5H, m, 3'-H, 5'-H, 3xPh-H); m/z 360 ($M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1624, 1614.

Example 70

6,7-Diacetoxy-4-(4-benzyloxyanilino)quinazoline

Aqueous hydrobromic acid (38%) (4 ml) was added to 6,7-dimethoxyquinazolin-4-(1H)-one (4-hydroxy-6, 7-dimethoxyquinazoline) (0.20 g, 0.97 mmol), and the mixture was stirred and heated at reflux for 10 h, after which a precipitate had formed. The mixture was cooled, filtered and the precipitate washed with diethyl ether/acetone (50:50) to give 6,7-dihydroxyquinazol-4-(1H)-one hydrobromide (0.23g, 92%) as a white solid, mp >360 °C (dec); (Found: C, 36.91; H, 2.68, N, 10.68. $C_8H_6N_2O_3.HBr$ requires: C, 37.09; H, 2.72; N, 10.81%); δH [$^2H_6$]-DMSO 8.99 (1H, s, 2-H), 7.44 (1H, s, 8-H), 7.18 (1H, s, 5-H); m/z (%) 178 (15, M^+), 73 (100).

A stirred mixture of 6,7-dihydroxyquinazol-4-(1H)-one hydrobromide (0.050 g, 0.19 mmol) and acetic anhydride (5 ml) was heated at reflux for 1 h and then cooled whereupon a white precipitate formed. The mixture was diluted with acetone and filtered. The precipitate was washed with diethyl ether to give 6,7-diacetoxyquinazol-4-(1H)-one hydrobromide (0.052 g, 75%), as a white solid, mp 257-260 °C (dec);(Found: C, 41.91; H, 3.19; N, 8.26. $C_{12}H_{10}N_2O_5.HBr$ requires: C, 41.98; H, 3.23; N, 8.16%); δH [$^2H_6$]-DMSO 8.26 (1H, s, Ar-H), 7.98 (1H, s, Ar-H), 7.60 (1H, s, Ar-H); m/z (%) 262 (10, M^+), 220 (40), 178 (100)

6,7-Diacetoxyquinazol-4-(1H)-one hydrobromide (0.50 g, 1.5 mmol) was mixed with thionyl chloride (10 ml) and heated to reflux for 2 h. The thionyl chloride was removed in vacuo to leave a yellow gum. To a portion of this gum (0.065 g, 0.22 mmol if pure) was added 4-benzyloxyaniline (0.088 g, 0.44 mmol) followed by acetone (2 ml). A yellow precipitate formed almost immediately and the mixture was stirred for 10 min. The mixture was diluted with acetone and the precipitate collected by filtration to leave most of the unwanted impurities in the filtrate (as

indicated by tlc). The yellow precipitate was dissolved in a mixture of dichloromethane (3 ml) and triethylamine (0.3 ml), and the volatiles were removed in vacuo. Chromatography (silica gel, ethyl acetate) gave 6,7-diacetoxy-4-(4-benzyloxyanilino)quinazoline (0.010 g, 10%) as a white solid, mp 195-196 °C; (Found: C, 66.29; H, 4.63, N, 9.39. $C_{25}H_{21}N_3O_5.0.5H_2O$ requires: C, 66.36; H, 4.90; N, 9.29%); δH [$^2H_6$]-DMSO 9.67 (1H, br s, NH), 8.52 (1H, s, 2-H or 8-H), 8.45 (1H, s, 2-H or 8-H), 7.72-7.62 (3H, m, 5-H, 2'-H, 6'-H), 7.49 (2H, d, J 8, 2"-H, 6"-H), 7.40 (3H, t, J 8, 3"-H, 5"-H), 7.35 (1H, t, J 8, 4"-H), 7.05 (2H, d, J 9, 3'-H, 5'-H), 5.12 (2H, s, OCH_2), 2.38 (6H, 2 x s, 2 x $OCOCH_3$); m/z (%) 444 (100, M+1$^+$); ν_{max} (KBr disc)/cm^{-1} 1774, 1574, 1533, 1510, 1427, 1211.

Example 71

6,7-Diethoxy-4-(3-phenoxy)anilinoquinazoline hydrochloride

4-Chloro-6,7-diethoxyquinazoline (0.126 g; 0.5 mmol) and 3-phenoxyaniline (0.111 g; 0.60 mmol) were reacted in 2-propanol (4 ml) for 35 minutes according to Procedure B. The product was thus obtained as pale yellow prisms (0.189 g, 86%) with mp 256-257°C (effervesc.); (Found C, 65.23; H, 5.48; N, 9.39. $C_{24}H_{23}N_3O_3.HCl.0.25H_2O$ requires C, 65.15; H, 5.54; N, 9.50); tlc (ethyl acetate) Rf 0.37; δH [$^2H_6$]-DMSO 11.34 (1H, br s, NH), 8.77 (1H, s, 2-H), 8.16 (1H, s, 8-H), 7.32-7.59 (5H, m, 5-H, 5'-H, 6'-H, 3"-H, 5"-H), 7.30 (1H, s, 2'-H), 7.19 (1H, t, J 9, 4"-H), 7.10 (2H, d, J 9, 2"-H, 6"-H), 6.93 (1H, d, J 9, 4'-H), 4.26 (4H, t, J 7, 2 x OCH_2), 1.42 (6H, t, J 7, 2 x CH_3); m/z (%) 401 (100, M+).

Example 72

6,7-Diethoxy-4-(4-phenoxy)anilinoquinazoline hydrochloride

4-Chloro-6,7-diethoxyquinazoline (0.126 g; 0.50 mmol) and 4-phenoxyaniline (0.111 g; 0.60 mmol) were reacted in 2-propanol (4 ml) for 30 minutes according to Procedure B. The product was thus obtained as pale yellow prisms (0.191 g, 87%) with mp 262-263°C; (Found C, 65.69; H, 5.53; N, 9.52. $C_{24}H_{23}N_3O_3.HCl$ requires C, 65.83; H, 5.48; N, 9.60); tlc (ethyl acetate) Rf 0.35; δH [$^2H_6$]-DMSO 11.20 (1H, br s, NH), 8.76 (1H, s, 2-H), 8.32 (1H, s, 8-H), 7.71 (2H, d, J 9, 2'-H, 6'-H), 7.37-7.50 (3H, m, 5-H, 3"-H, 5"-H), 7.03-7.23 (5H, m, 3'-H, 5'-H, 2"-H, 4"-H, 6"-H), 4.20-4.39 (4H, m, 2 x OCH_2), 1.40-1.53 (6H, m, 2 x CH_3); m/z (%) 401 (100, M+).

Example 73

4-(4-Benzyloxy)anilino-6,7-diethoxyquinazoline hydrochloride

4-Chloro-6,7-diethoxyquinazoline (0.089 g; 0.35 mmol) and 4-benzyloxyaniline (0.080 g; 0.40 mmol) were reacted in 2-propanol (3 ml) for 30 minutes according to Procedure B. The product was thus obtained as small yellow needles (0.150 g, 95%) with mp 264-265°C (effervesc.); (Found C, 66.12; H, 5.71; N, 9.11. $C_{25}H_{25}N_3O_3$.HCl requires C, 66.44; H, 5.76; N, 9.30); tlc (ethyl acetate) Rf 0.40; δH [$^2H_6$]-DMSO 11.16 (1H, br s, NH), 8.71 (1H, s, 2-H), 8.28 (1H, s, 8-H), 7.59 (2H, d, J 9, 2'-H, 6'-H), 7.29-7.53 (6H, m, 5-H, 5 x PhH), 7.10 (2H, d, J 9, 3'-H, 5'-H), 5.16 (2H, s, CH_2), 4.20-4.36 (4H, m, 2 x OCH_2), 1.38-1.50 (6H, m, 2 x CH_3); m/z (%) 415 (20, M+), 324 (100).

Example 74

6,7-Methylenedioxy-4-(3-phenoxyanilino)quinazoline hydrochloride

4-Chloro-6,7-methylenedioxyquinazoline (0.113 g; 0.50 mmol) and 3-phenoxyaniline (0.102 g; 0.55 mmol) were reacted in 2-propanol (3.5 ml) for 40 minutes according to procedure B. The product was thus obtained as cream prisms (0.194 g, 99%) with mp 300-302°C; (Found C, 63.93; H, 4.07; N, 10.64. $C_{21}H_{15}N_3O_3$.HCl requires C, 64.04; H, 4.07; N, 10.67); tlc (ethyl acetate) Rf 0.54; δH [$^2H_6$]-DMSO 10.75 (1H, br s, NH), 8.79 (1H, s, 2-H), 8.26 (1H, s, 8-H), 7.59 (1H, d, J 9, 6'-H), 7.31-7.51 (5H, m, 5-H, 2'-H, 5'-H, 3"-H, 5"-H), 7.20 (1H, t, J 8, 4"-H), 7.09 (2H, d, J 9, 2"-H, 6"-H), 6.92 (1H, d, J 8, 4'-H), 6.39 (2H, s, CH_2O_2); m/z (%) 358 (100, $M+1^+$).

Example 75

6,7-Methylenedioxy-4-(4-phenoxyanilino)quinazoline hydrochloride

4-Chloro-6,7-methylenedioxyquinazoline (0.113 g; 0.50 mmol) and 4-phenoxyaniline (0.102 g; 0.55 mmol) were reacted in 2-propanol (3.5 ml) for 45 minutes according to Procedure B. The product was thus obtained as pale yellow plates (0.192 g, 98%) with mp 283-285°C; (Found C, 64.00; H, 4.10; N, 10.70. $C_{21}H_{15}N_3O_3$.HCl requires C, 64.04; H, 4.07; N, 10.67); tlc (ethyl acetate) Rf 0.51; δH [$^2H_6$]-DMSO 10.97 (1H, br s, NH), 8.75 (1H, s, 2-H), 8.30 (1H, s, 8-H), 7.71 (2H, d, J 9, 2'-H, 6'-H), 7.37-7.49 (3H, m, 5-H, 3'-H, 5'-H), 7.04-7.21 (5H, m, 3'-H, 5'-H, 2"-H, 4"-H, 6"-H), 6.39 (2H, s, CH_2O_2); m/z (%) 358 (100, $M+1^+$).

Example 76

4-(4-Benzyloxyanilino)-6,7-methylenedioxyquinazoline hydrochloride

4-Chloro-6,7-methylenedioxyquinazoline (0.113 g; 0.50 mmol) and 4-benzyloxyaniline (0.109 g; 0.55 mmol) were reacted in 2-propanol (3.5 ml) for 50 minutes according to procedure B. The product was thus obtained as yellow prisms (0.201 g, 99%) with mp 297-299°C; (Found C, 64.34; H, 4.36; N, 10.34. $C_{22}H_{17}N_3O_3$.HCl requires C, 64.78;

H, 4.42; N, 10.30); tlc (ethyl acetate) Rf 0.50; δH [$^2H_6$]-DMSO 11.03 (1H, br s, NH), 8.72 (1H, s, 2-H), 8.31 (1H, s, 8-H), 7.60 (2H, d, J 9, 2'-H, 6'-H), 7.30-7.52 (6H, m, 5-H, 5 x PhH), 7.10 (2H, d, J 9, 3'-H, 5'-H), 6.40 (2H, s, CH_2O_2), 5.15 (2H, s, CH_2); m/z (%) 372 (100, M+1$^+$).

Example 77

6,7-Dimethoxy-2-methyl-4-(3-phenoxyanilino)quinazoline hydrochloride

4-Chloro-6,7-dimethoxy-2-methylquinazoline (0.084 g; 0.35 mmol) and 3-phenoxyaniline (0.074 g; 0.40 mmol) were reacted in 2-propanol (2.5 ml) for 40 minutes according to Procedure B. The product was thus obtained as pale cream prisms (0.137 g, 92%) with mp 261-263°C (effervesc.); (Found C, 64.40; H, 5.25; N, 9.50. $C_{23}H_{21}N_3O_3$.HCl.0.25H_2O requires C, 64.48; H, 5.26; N, 9.81); tlc (ethyl acetate) Rf 0.27; δH [$^2H_6$]-DMSO 11.03 (1H, br s, NH), 8.20 (1H, s, 8-H), 7.38-7.60 (5H, m, 5-H, 5'-H, 6'-H, 3"-H, 5"-H), 7.29 (1H, s, 2'-H), 7.19 (1H, t, J 8, 4"-H), 7.10 (2H, d, J 9, 2"-H, 6"-H), 6.97 (1H, d, J 9, 4'-H), 4.02 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3), 2.53 (3H, s, 2-CH_3); m/z (%) 388 (100, M+1$^+$).

Example 78

6,7-Dimethoxy-2-methyl-4-(4-phenoxyanilino)quinazoline hydrochloride

4-Chloro-6,7-dimethoxy-2-methyl quinazoline (0.084 g; 0.35 mmol) and 4-phenoxyaniline (0.074 g; 0.40 mmol) were reacted in 2-propanol (2.5 ml) for 35 minutes according to Procedure B. The product was thus obtained as a dark cream powder (0.142 g, 96%) with mp 260-261°C (effervesc.); (Found C, 64.42; H, 5.19; N, 9.66. $C_{23}H_{21}N_3O_3$.HCl.0.25 H_2O requires C, 64.48; H, 5.26; N, 9.81); tlc (ethyl acetate) Rf 0.23; δH [$^2H_6$]-DMSO 11.25 (1H, br s, NH), 8.30 (1H, s, 8-H), 7.75 (2H, d, J 9, 2'-H, 6'-H), 7.43 (2H, t, J 8, 3"-H, 5"-H), 7.36 (1H, s, 5-H), 7.03-7.24 (5H, m, 3'-H, 5'-H, 2"-H, 4"-H, 6"-H), 4.03 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3), 2.61 (3H, s, 2-CH_3); m/z (%) 388 (100, M+1$^+$).

Example 79

4-(4-Benzyloxyanilino)-6,7-dimethoxy-2-methylquinazoline hydrochloride

4-Chloro-6,7-dimethoxy-2-methylquinazoline (0.084 g; 0.35 mmol) and 4-benzyloxyaniline (0.080 g; 0.40 mmol) were reacted in 2-propanol (2.5 ml) for 40 minutes according to Procedure B. The product was thus obtained as mustard prisms (0.149 g, 97%) with mp 270-271°C (dec.); (Found C, 64.93; H, 5.55; N, 9.24. $C_{24}H_{23}N_3O_3$.HCl.0.33H_2O requires C, 64.93; H, 5.56; N, 9.47); tlc (ethyl acetate) Rf 0.18; δH [$^2H_6$]-DMSO 11.00 (1H, br s, NH), 8.20 (1H, s, 8-H), 7.62 (2H, s, J 9, 2'-H,

6'-H), 7.39-7.50 (5H, m. 5 x PhH) 7.25 (1H, s, 5H), 7.11 (2H, d, J 9, 3'-H, 5'-H), 5.17 (2H. s, CH_2), 4.01 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3), 2.57 (3H, s, 2-CH_3); m/z (%) 402 (100, $M+1^+$).

Example 80

4-(4-Benzylaminoanilino)quinazoline hydrochloride

4-Benzamidoaniline was prepared from 4-nitroaniline (commercially available) according to the published method (D. L. Boger and H. Zarrinmayeh, J. Org. Chem., 55, 1379, (1990)).

A 1.0M solution of lithium aluminium hydride in tetrahydrofuran (8.0 ml, 8.0 mmol) was added dropwise over a period of 5 minutes to a solution of 4-benzamidoaniline (0.82 g, 3.9 mmol) in tetrahydrofuran (30 ml) under nitrogen at room temperature. The orange mixture was then heated at reflux for 12 hours. Water (0.7 ml) followed by 15% aq.NaOH (0.5 ml) and then water (2 ml) was cautiously added to the ice cooled mixture forming a precipitate. This mixture was diluted with dichloromethane (30 ml) and filtered to remove the precipitate. The filtrate was concentrated in vacuo and the residue chromatographed (silica gel, 2% methanol/dichloromethane) to give 4-benzylaminoaniline (0.52 g, 67%) as a deep red solid; δH [$^2H_3$]-$CDCl_3$ 7.38-7.20 (5H, m, 5 x PhH), 6.59 and 6.52 (2 x 2H, 2 x d, J 9, 2-H and 6-H, 3-H and 5-H), 4.27 (2H, s, CH_2), 3.30 (3H, br s, NH_2, NH); m/z (%) 198 (75, M^+), 107 (100).

4-Chloroquinazoline (0.15 g, 0.91 mmol) and 4-benzylaminoaniline (0.15 g, 0.76 mmol) were reacted in 2-propanol (15 ml) for 30 minutes according to Procedure B. The yellow solid thus obtained was 4-(4-benzylaminoanilino)quinazoline hydrochloride (0.17 g, 62%), mp 210°C (dec); (Found: C, 68.76; H, 5.09 N, 15.14. $C_{21}H_{18}N_4.HCl.0.2H_2O$ requires: C, 68.83; H, 5.33; N, 15.28%); δH [$^2H_6$]-DMSO 11.25 (1H, br s, NH), 8.78 (1H, s, 2-H), 8.70 (1H, d, J 8, 8-H), 8.02 (1H, t, J 8, 7-H), 7.86 (1H, d, J 8, 5-H), 7.80 (1H, t, J 8, 6-H), 7.41-7.30 (6H, m, 2'-H, 6'-H, 2"-H, 3"-H, 5"-H, 6"-H), 7.23 (1H, t, J 8, 4"-H), 6.68 (2H, d, J 9, 3'-H, 5'-H), 4.32 (2H, s, CH_2); m/z (%) 327 (100, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1630, 1612, 1568, 1520, 1373, 762.

Example 81

4-(4-Benzylaminoanilino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.12 g, 0.54 mmol) and 4-benzylaminoaniline (prepared as described above) (0.15 g, 0.76 mmol) were reacted in 2-propanol (15 ml) for 30 minutes according to Procedure B. The yellow solid thus obtained was 4-

(4-benzylaminoanilino)-6,7-dimethoxyquinazoline hydrochloride (0.16 g, 70%), mp 255-256 °C; (Found: C, 65.59; H, 5.67 N, 13.30. $C_{23}H_{22}N_4O_2$.HCl requires: C, 65.32; H, 5.48; N, 13.25%); δH [$^2H_6$]-DMSO 11.07 (1H, br s, NH), 8.65 (1H, s, 2-H), 8.20 (1H, s, 8-H), 7.42-7.28 (7H, m, 5-H, 2'-H, 6'-H, 2"-H, 3"-H, 5"-H, 6"-H), 7.23 (1H, t, J 8, 4"-H), 6.67 (2H, d, J 9, 3'-H, 5'-H), 4.32 (2H, s, CH_2), 3.96 (6H, s, 2 x OCH_3); m/z (%) 387 (100, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1630, 1576, 1514, 1437, 1277.

Example 82

4-(4-Benzylanilino)quinazoline hydrochloride

4-Chloroquinazoline (0.10 g, 0.61 mmol) and 4-aminodiphenylmethane (commercially available) (0.16 g, 0.85 mmol) were reacted in 2-propanol (15 ml) for 30 minutes according to Procedure B, except that crystallisation was induced by the addition of diethyl ether. The pale creamy yellow solid thus obtained was 4-(4-benzylanilino)quinazoline hydrochloride (0.13 g, 62%), mp 235-236 °C; (Found: C, 72.23; H, 5.19 N, 11.93. $C_{21}H_{17}N_3$.HCl requires: C, 72.51; H, 5.22; N, 12.08%); δH [$^2H_6$]-DMSO 11.54 (1H, br s, NH), 8.91 (1H, d, J 8, 8-H), 8.87 (1H, s, 2-H), 8.08 (1H, t, J 8, 7-H), 7.96 (1H, d, J 8, 5-H), 7.84 (1H, t, J 8, 6-H), 7.63 (2H, d, J 9, 2'-H, 6'-H) 7.38-7.24 (6H, m, 3'-H, 5'-H, 2"-H, 3"-H, 5"-H, 6"-H), 7.20 (1H, t, J 8, 4"-H), 4.00 (2H, s, CH_2); m/z (%) 312 (100, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1632, 1614, 1562, 1433, 1375.

Example 83

4-(4-Benzylanilino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.10 g, 0.45 mmol) and 4-aminodiphenylmethane (0.12 g, 0.67 mmol) were reacted in 2-propanol (12 ml) for 30 minutes according to Procedure B, except that crystallisation was induced by the addition of diethyl ether. The colourless solid thus obtained was 4-(4-benzylanilino)-6,7-dimethoxyquinazoline hydrochloride (0.14 g, 77%), mp 259-260 °C; (Found: C, 67.94; H, 5.50 N, 10.29. $C_{23}H_{21}N_3O_2$.HCl requires: C, 67.73; H, 5.44; N, 10.30%); δH [$^2H_6$]-DMSO 11.40 (1H, br s, NH), 8.74 (1H, s, 2-H), 8.34 (1H, s, 8-H), 7.61 (2H, d, J 9, 2'-H, 6'-H), 7.40 (1H, s, 5-H), 7.35-7.25 (6H, m, 3'-H, 5'-H, 2"-H, 3"-H, 5"-H, 6"-H), 7.21 (1H, t, J 8, 4"-H), 4.00 (6H, s, 2 x OCH_3), 3.98 (2H, s, CH_2); m/z (%) 372 (100, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1632, 1576, 1512, 1437, 1281.

Example 84

4-(4-Benzylanilino)-6,7-diethoxyquinazoline hydrochloride

4-Chloro-6,7-diethoxyquinazoline (0.126 g; 0.30 mmol) and 4-benzylaniline (0. 92 g; 0.50 mmol) were reacted in 2-propanol (2.5 ml) for 20 minutes according to Procedure B. The product was thus obtained as pale yellow needles (0.189 g, 87%) with mp 242-244°C; (Found C, 68.80; H, 5.90; N, 9.54. $C_{25}H_{25}N_3O_2$.HCl requires C, 68.88; H, 5.97; N, 9.64); tlc (ethyl acetate) Rf 0.42; δH [$^2H_6$]-DMSO 11.23 (1H, br s, NH), 8.71 (1H, s, 2-H), 8.29 (1H, s, 8-H), 7.60 (2H, d, J 9, 2'-H, 6'-H), 7.16-7.40 (8H, m, 5'-H, 3'-H, 5'-H, 5 x PhH), 4.20-4.38 (4H, m, 2 x OCH_2), 4.04 (2H, s, CH_2), 1.37-1.51 (6H, m, 2 x CH_3); m/z (%) 399 (100, M+).

Example 85

4-(4-Benzylanilino)-6,7-methylenedioxyquinazoline hydrochloride

4-Chloro-6,7-methylenedioxyquinazoline (0.113 g; 0.50 mmol) and 4-benzylaniline (0.101 g; 0.55 mmol) were reacted in 2-propanol (3.5 ml) for 60 minutes according to procedure B. The product was thus obtained as pale mustard prisms (0.191 g, 97%) with mp 296-298°C; (Found C, 67.26; H, 4.64; N, 10.67. $C_{22}H_{17}N_3O_2$.HCl requires C, 67.43; H, 4.60; N, 10.73); tlc (ethyl acetate) Rf 0.50; δH [$^2H_6$]-DMSO 10.98 (1H, br s, NH), 8.71 (1H, s, 2-H), 8.30 (1H, s, 8-H), 7.61 (2H, d, J 9, 2'-H, 6'-H), 7.40 (1H, s, 5-H), 7.17-7.32 (7H, m, 3'-H, 5'-H, 5 x PhH), 6.39 (2H, s, CH_2O_2), 4.00 (2H, s, CH_2); m/z (%) 356 (100, $M+1^+$).

Example 86

4-(4-Benzylanilino)-6-bromoquinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.122 g; 0.50 mmol) and 4-benzylaniline (0.092 g; 0.50 mmol) were reacted in 2-propanol (2.5 ml) for 30 minutes according to Procedure B. The product was thus obtained as bright yellow prisms (0.194 g, 91%) with mp 264-266°C; (Found C, 59.12; H, 4.04; N, 9.71. $C_{21}H_{16}BrN_3$.HCl requires C, 59.08; H, 3.98; N, 9.85); tlc (ethyl acetate) Rf 0.60; δH [$^2H_6$]-DMSO 11.60 (1H, br s, NH), 9.23 (1H, s, 5-H), 8.88 (1H, s, 2-H), 8.21 (1H, d, J 9, 7-H), 7.93 (1H, d, J 9, 8-H), 7.68 (2H, d, J 8, 2'-H, 6'-H), 7.21-7.40 (7H, m, 3'-H, 5'-H, 5 x PhH), 4.00 (2H, s, CH_2); m/z (%) 390 (100, M+).

Example 87

4-(4-Benzylanilino)-6,7-dimethoxy-2-methylquinazoline hydrochloride

4-Chloro-6,7-dimethoxy-2-methylquinazoline (0.084 g; 0.35 mmol) and 4-benzylaniline (0.073 g; 0.40 mmol) were reacted in 2-propanol (2.5 ml) for 50 minutes according to Procedure B. The product was thus obtained as beige prisms (0.124 g, 84%) with mp

269-270°C (effervesc.); (Found C, 67.80; H, 5.70; N, 9.74. $C_{24}H_{23}N_3O_2.HCl.0.25H_2O$ requires C, 67.60; H, 5.75; N, 9.86); tlc (ethyl acetate) Rf 0.22; δH [$^2H_6$]-DMSO 11.08 (1H, br s, NH), 8.22 (1H, s, 8-H), 7.14 (2H, d, J 9, 2'-H, 6'-H), 7.17-7.37 (8H, m, 5-H, 3'-H, 5'-H, 5 x PhH), 4.03 (2H, s, CH_2), 4.02 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3), 2.59 (3H, s, 2-CH_3); m/z (%) 386 (100), M+1$^+$).

Example 88

4-(4-Anilinoanilino)quinazoline hydrochloride

4-Chloroquinazoline (0.13 g, 0.76 mmol) and 4-anilinoaniline (Aldrich) (0.18 g, 0.91 mmol) were reacted in 2-propanol (12 ml) for 30 minutes according to Procedure B. The rusty brown solid thus obtained was 4-(4-anilinoanilino)quinazoline hydrochloride (0.25 g, 93%), mp 246-248°C; (Found: C, 68.21; H, 4.91; N, 15.57. $C_{20}H_{16}N_4.HCl$ 0.25 H_2O requires: C, 67.99; H, 4.95; N, 15.86%); δH [$^2H_6$]-DMSO 11.55 (1H, br s, NH), 8.93 (1H, d, J 8, 8-H), 8.87 (1H, s, 2-H), 8.30 (1H, br s, NH), 8.08 (1H, t, J 8, 7-H), 7.95 (1H, d, J 8, 5-H), 7.82 (1H, t, J 8, 6-H), 7.60 (2H, d, J 9, 2'-H, 6'-H) 7.25 (2H, t, J 9, 3"-H, 5"-H), 7.15 (4H, m, 3'-H, 5'-H, 2"-H, 6"-H), 6.87 (1H, t, J 9, 4"-H); m/z (%) 313 (100, M+1$^+$); νmax (KBr disc)/cm^{-1} 1632, 1614, 1595, 1520, 1493.

Example 89

4-(4-Anilinoanilino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.061 g, 0.27 mmol) and 4-anilinoaniline (Aldrich) (0.075 g, 0.41 mmol) were reacted in 2-propanol (6 ml) for 30 minutes according to Procedure B. The olive green solid thus obtained was 4-(4-anilinoanilino)-6,7-dimethoxyquinazoline hydrochloride (0.088 g, 79%), mp 266-268°C; (Found: C, 64.54; H, 5.24; N, 13.63. $C_{22}H_{20}N_4O_2.HCl$ requires: C, 64.62; H, 5.18; N, 13.70%); δH [$^2H_6$]-DMSO 11.20 (1H, br s, NH), 8.75 (1H, s, 2-H), 8.27 (1H, s, 8-H), 8.27 (1H, br s, NH), 7.54 (2H, d, J 9, 2'-H, 6'-H), 7.36 (1H, s, 5-H), 7.27 (2H, t, J 8, 3"-H, 5"-H), 7.17-7.10 (4H, m, 3'-H, 5'-H, 2"-H, 6"-H), 6.85 (1H, t, J 8, 4"-H), 4.00 (6H, s, 2 x CH_3); m/z (%) 373 (100, M+1$^+$); νmax (KBr disc)/cm^{-1} 1632, 1595, 1574, 1512, 1495, 1437.

Example 90

4-(4-Benzoylanilino)quinazoline hydrochloride

4-Chloroquinazoline (0.10 g, 0.61 mmol) and 4-aminobenzophenone (Aldrich) (0.18 g, 0.91 mmol) were reacted in 2-propanol (12 ml) for 30 minutes according to Procedure B. The pale yellow solid thus obtained was 4-(4-

benzoylanilino)quinazoline hydrochloride (0.20 g, 91%), mp 288°C (dec); (Found: C, 69.30; H, 4.41; N, 11.42. $C_{21}H_{15}N_3O.HCl.0.1H_2O$ requires: C, 69.36; H, 4.49; N, 11.56%); δH [$^2H_6$]-DMSO 11.95 (1H, br s, NH), 9.18 (1H, d, J 9, 8-H), 9.12 (1H, s, 2-H), 8.25 (1H, t, J 8, 7-H), 8.22-8.15 (3H, m, 3'-H, 5'-H, 5-H), 8.05-7.95 (3H, m, 2'-H, 6'-H, 6-H), 7.88 (2H, d, J 8, 2"-H, 6"-H) 7.80 (1H, t, J 8, 4"-H), 7.72 (2H, t, J 8, 3"-H, 5"-H); m/z (%) 325 (100, M^+); ν_{max} (KBr disc)/cm^{-1} 1655, 1634, 1601, 1564, 1533.

Example 91

4-(4-Benzoylanilino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.102 g, 0.454 mmol) and 4-aminobenzophenone (Aldrich) (0.11 g, 0.545 mmol) were reacted in 2-propanol (15 ml) for 4 h according to Procedure B. The pale yellow solid thus obtained was 4-(4-benzoylanilino)-6,7-dimethoxyquinazoline hydrochloride (0.16 g, 84%), mp 264-265°C; (Found: C, 65.72; H, 4.73; N, 9.87. $C_{23}H_{19}N_3O_3.HCl$ requires: C, 65.48; H, 4.78; N, 9.96%); δH [$^2H_6$]-DMSO 11.40 (1H, br s, NH), 8.80 (1H, s, 2-H), 8.38 (1H, s, 8-H), 8.01 (2H, d, J 9, 3'-H, 5'-H), 7.87 (2H, d, J 9, 2'-H, 6'-H), 7.77 (2H, m, 2"-H, 6"-H), 7.70 (1H, t, J 9, 4"-H), 7.59 (2H, t, J 9, 3"-H, 5"-H), 7.40 (1H, s, 5-H), 4.02 (6H, 2 x s, 2 x CH_3); m/z (%) 385 (68, M^+), 384 (100); ν_{max} (KBr disc)/cm^{-1} 2600, 1653, 1632, 1599, 1572, 1516, 1451, 1277, 1230.

Example 92

4-(4-Benzoylaminoanilino)quinazoline hydrochloride

4-Chloroquinazoline (0.10 g, 0.61 mmol) and 4-benzamidoaniline (Salor via Aldrich) (0.15 g, 0.71 mmol) were reacted in 2-propanol (12 ml) for 30 minutes according to Procedure B. The bright yellow solid thus obtained was 4-(4-benzoylaminoanilino)quinazoline hydrochloride (0.19 g, 82%), mp 322-324°C; (Found: C, 66.21; H, 4.56; N, 14.58. $C_{21}H_{16}N_4O.HCl.0.2\ H_2O$ requires: C, 66.30; H, 4.61; N, 14.73%); δH [$^2H_6$]-DMSO 11.71 (1H, br s, NH), 10.40 (1H, s, NHCO), 8.97 (1H, d, J 9, 8-H), 8.90 (1H, s, 2-H), 8.10 (1H, t, J 8, 7-H), 8.05-7.97 (3H, m, 5-H, 2"-H, 6"-H,), 7.91 (2H, d, J 9, 2'-H, 6'-H), 7.85 (1H, t, J 8, 6-H),7.74 (2H, d, J 9, 3'-H, 5'-H), 7.58 (1H, t, J 8, 4"-H), 7.53 (2H, t, J 9, 3"-H, 5"-H); m/z (%) 340 (80, M^+), 105 (100); ν_{max} (KBr disc)/cm^{-1} 1653, 1634, 1612, 1566, 1514, 1429, 1357.

Example 93

4-(4-Benzoylaminoanilino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.102 g, 0.454 mmol) and 4-benzamidoaniline (Salor via Aldrich) (0.116 g, 0.546 mmol) were reacted in 2-propanol (15 ml) for 1 h according to Procedure B. The pale yellow solid thus obtained was 4-(4-benzoylaminoanilino)-6,7-dimethoxyquinazoline hydrochloride (0.110 g, 55%), mp 266-267°C; (Found: C, 62.82; H, 4.71; N, 12.48. $C_{23}H_{20}N_4O_3.HCl.0.15H_2O$ requires: C, 62.84; H, 4.88; N, 12.74%); δH [$^2H_6$]-DMSO 11.17 (1H, br s, NH), 10.35 (1H, s, NHCO), 8.78 (1H, s, 2-H), 8.25 (1H, s, 8-H), 7.95 (2H, d, J 9, 2"-H, 6"-H), 7.88 (2H, d, J 9, 2'-H, 6'-H), 7.67 (2H, d, J 9, 3'-H, 5'-H), 7.61 (1H, t, J 8, 4"-H), 7.52 (2H, t, J 8, 3"-H, 5"-H), 7.33 (1H, s, 5-H), 4.02 (6H, 2 x s, 2 x CH_3); m/z (%) 400 (82, M^+), 105 (100); ν_{max} (KBr disc)/cm^{-1} 1632, 1578, 1512, 1437, 1279.

Example 94

4-(4-Anilinocarbonylanilino)quinazoline hydrochloride

4-Chloroquinazoline (0.10 g, 0.61 mmol) and 4-aminobenzanilide (APIN) (0.15 g, 0.69 mmol) were reacted in 2-propanol (15 ml) for 15 minutes according to Procedure B. The creamy yellow solid thus obtained was 4-(4-anilinocarbonylanilino)quinazoline hydrochloride (0.19 g, 83%), mp 326-327 °C; (Found: C, 66.28; H, 4.44; N, 14.56. $C_{21}H_{16}N_4O.HCl.0.2H_2O$ requires: C, 66.30; H, 4.60; N, 14.73%); δH [$^2H_6$]-DMSO 11.87 (1H, br s, NH), 10.40 (1H, s, NHCO), 9.12 (1H, d, J 9, 8-H), 9.08 (1H, s, 2-H), 8.20-8.17 (3H, m, 7-H, 3'-H, 5'-H), 8.12 (1H, d, J 9, 5-H), 8.06 (2H, d, J 9, 2'-H, 6'-H), 7.96 (1H, t, J 8, 6-H), 7.92 (2H, d, J 9, 2"-H, 6"-H), 7.48 (2H, t, J 9, 3"-H, 5"-H), 7.22 (1H, t, J 9, 4"-H); m/z (%) 340 (22, M^+), 248 (100); ν_{max} (KBr disc)/cm^{-1} 1666, 1634, 1605, 1560, 1535, 1508, 1497, 1439, 1377, 1319.

Example 95

4-(4-Anilinocarbonylanilino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.10 g, 0.45 mmol) and 4-aminobenzanilide (APIN) (0.12 g, 0.58 mmol) were reacted in 2-propanol (15 ml) for 30 min according to Procedure B. The pale cream solid thus obtained was 4-(4-anilinocarbonylanilino)-6,7-dimethoxyquinazoline hydrochloride (0.16 g, 79%), mp 275-277 °C; (Found: C, 62.38; H, 4.72; N, 12.60. $C_{23}H_{20}N_4O_3.HCl.0.3H_2O$ requires: C, 62.46; H, 4.92; N, 12.67%); δH [$^2H_6$]-DMSO 11.50 (1H, br s, NH), 10.25 (1H, s, NHCO), 8.86 (1H, s, 2-H), 8.41 (1H, s, 8-H), 8.08 (2H, d, J 9, 3'-H, 5'-H), 7.95 (2H, d, J 9, 2'-H, 6'-H), 7.80 (2H, d, J 9, 2"-H, 6"-H), 7.42 (1H, s, 5-H), 7.37 (2H, t, J 9, 3"-H, 5"-H), 7.10 (1H, t, J 9, 4"-H), 4.02 (6H, 2 x s, 2 x CH_3); m/z

(%) 400 (20, M^+), 308 (100); ν_{max} (KBr disc)/cm^{-1} 1664, 1635, 1597, 1578, 1527, 1510, 1437, 1277, 1236.

Example 96

4-(4-Anilinomethylanilino)quinazoline hydrochloride

A solution of 4-aminobenzanilide (APIN) (1.0 g, 4.7 mmol) in dry tetrahydrofuran (10 ml) was carefully added to a stirred suspension of lithium aluminium hydride (0.27 g, 7.05 mmol) under an atmosphere of nitrogen over a period of 20 min. The mixture was then heated to reflux for 2 h. Further lithium aluminium hydride was added as a 1.0 M solution in tetrahydrofuran (4.0 ml, 4.0 mmol), and the mixture heated at reflux for a further 5 h. Water (1.0 ml) was then carefully added to the ice-cooled green mixture, followed by 15% aq. sodium hydroxide (1.0 ml), and further water (3.0 ml). The crystalline precipitate was then diluted with dichloromethane (25 ml) and then filtered. The filtrate was evaporated in vacuo, and the residual brown oil chromatographed (silica gel, 5% methanol/dichlormethane) to give 4-anilinomethylaniline (0.54 g, 59%) as a light brown solid; δH $CDCl_3$ 7.20-7.10 (4H, m, 3-H, 5-H, 3'-H, 5'-H), 6.70 (1H, t, J 9, 4-H), 6.68-6.60 (4H, m, 2-H, 6-H, 2'-H, 6'-H).

4-Chloroquinazoline (0.10 g, 0.61 mmol) and 4-anilinomethylaniline (0.16 g, 0.82 mmol) were reacted in 2-propanol (15 ml) for 30 minutes according to Procedure B. The bright yellow solid thus obtained was 4-(4-anilinomethylanilino)quinazoline hydrochloride (0.16 g, 72%), mp 198-200 °C; (Found: C, 68.64; H, 5.13; N, 15.16. $C_{21}H_{18}N_4.HCl.0.3H_2O$ requires: C, 68.49; H, 5.36; N, 15.21%); δH [$^2H_6$]-DMSO 11.52 (1H, br s, NH), 8.98 (1H, d, J 9, 8-H), 8.87 (1H, s, 2-H), 8.08 (1H, t, J 9, 6-H), 7.96 (1H, d, J 9, 5-H), 7.82 (1H, t, J 9, 7-H), 7.67 (2H, d, J 9, 2'-H, 6'-H), 7.49 (2H, t, J 9, 3'-H, 5'-H), 7.08 (2H, d, J 9, 3"-H, 5"-H), 6.64 (2H, t, J 9, 2"-H, 6"-H), 6.58 (1H, t, J 9, 4"-H), 4.30 (2H, s, CH_2N); m/z (%) 326 (19, M^+), 234 (100); ν_{max} (KBr disc)/cm^{-1} 2642, 1634, 1605, 1562, 1510, 1435, 1375.

Example 97

4-(4-Phenylethynylanilino)quinazoline hydrochloride

Bis(triphenylphosphine)palladium(II) chloride (0.12 g, 0.17 mmol) was added to a stirred solution of phenylacetylene (Aldrich) (1.3 g, 12.7 mmol) and 4-iodoaniline (Aldrich) (2.14 g, 9.8 mmol) in triethylamine (50 ml) at room temperature under nitrogen, followed immediately by copper iodide (0.04g, 0.21 mmol). The reaction vessel was covered with aluminium foil to prevent exposure to light, and the

mixture was stirred for 1 h. The dark mixture was then evaporated, and the residue chromatographed (silica gel, gradient elution from 50% petrol (40-60) in dichloromethane to 100% dichloromethane) to give the product 4-phenylethynylaniline (1.49 g, 61%) as a light brown solid, δH [$^2H_6$]-DMSO 7.45 (2H, d, J 9, 2'-H, 6'-H), 7.42-7.30 (3H, m, 4'-H, 3'-H, 5'-H), 7.20 (2H, d, J 9, 3-H, 5-H), 6.57 (2H, d, J 9, 2-H, 6-H), 5.48 (2H, br s, NH_2).

4-Chloroquinazoline (0.10 g, 0.61 mmol) and 4-phenylethynylaniline (0.16 g, 0.83 mmol) were reacted in 2-propanol (12 ml) for 15 minutes according to Procedure B. The pale yellow solid thus obtained was 4-(4-phenylethynylanilino)quinazoline hydrochloride (0.18 g, 83%), mp 259-261°C; (Found: C, 73.61; H, 4.56; N, 11.57. $C_{22}H_{15}N_3$.HCl requires: C, 73.84; H, 4.51; N, 11.74%); δH [$^2H_6$]-DMSO 11.60 (1H, br s, NH), 8.92 (1H, d, J 9, 8-H), 8.87 (1H, s, 2-H), 8.02 (1H, t, J 8, 7-H), 7.94 (1H, d, J 8, 5-H), 7.84 (2H, d, J 9, 3'-H, 5'-H), 7.77 (1H, t, J 8, 6-H), 7.60 (2H, d, J 9, 2'-H, 6'-H), 7.50 (2H, t, J 9, 2"-H, 6"-H), 7.45-7.30 (3H, m, 3"-H, 4"-H, 5"-H); m/z (%) 321 (100, M^+); ν_{max} (KBr disc)/cm^{-1} 1630, 1612, 1587, 1566, 1556, 1535, 1423.

Example 98

6,7-Dimethoxy-4-(4-phenylethynylanilino)quinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.102 g, 0.454 mmol) and 4-phenylethynylaniline (0.116 g, 0.545 mmol) were reacted in dry dimethylformamide (5 ml) for 2 h according to Procedure B. The yellow solid thus obtained was 6,7-dimethoxy-4-(4-phenylethynylanilino)quinazoline hydrochloride (0.20 g, 97%), mp 267-269°C; (Found: C, 69.38; H, 4.88; N, 9.62; Cl, 8.35. $C_{24}H_{19}N_3O_2$.HCl requires: C, 68.98; H, 4.79; N, 10.06; Cl, 8.50%); δH [$^2H_6$]-DMSO 11.20 (1H, br s, NH), 8.82 (1H, s, 2-H), 8.28 (1H, s, 8-H), 7.85 (2H, d, J 9, 3'-H, 5'-H), 7.68 (2H, d, J 9, 2'-H, 6'-H), 7.58 (2H, m, 2"-H, 6"-H), 7.42 (3H, m, 4"-H, 3"-H, 5"-H), 7.35 (1H, s, 5-H), 4.02 (6H, 2 x s, 2 x CH_3); m/z (%) 381 (100, M^+), 105 (100).

Example 99

(trans)-4-(4-Phenylethenyl)anilinoquinazoline hydrochloride

4-Chloroquinazoline (0.10 g, 0.61 mmol) and 4-aminostilbene (TCI) (0.15 g, 0.79 mmol) were reacted in 2-propanol (15 ml) for 3 minutes according to Procedure B. The yellow solid thus obtained was (trans)-4-(4-phenylethenyl)anilinoquinazoline hydrochloride (0.15 g, 68%), mp 305-307 °C; (Found: C, 73.01; H, 5.12; N, 11.51. $C_{22}H_{17}N_3$.HCl.0.1H_2O requires: C, 73.06; H, 5.07; N, 11.61%); δH [$^2H_6$]-DMSO 11.62 (1H, br s, NH), 8.95 (1H, d, J 9, 8-H), 8.92 (1H, s, 2-H), 8.11 (1H, t, J 9, 6-H),

7.99 (1H, d, J 9, 5-H), 7.88 (1H, t, J 9, 7-H), 7.82 (2H, d, J 9, 3'-H, 5'-H), 7.73 (2H, t, J 9, 2'-H, 6'-H), 7.62 (2H, d, J 9, 2"-H, 6"-H), 7.40 (2H, t, J 9, 3"-H, 5"-H), 7.32-7.25 (3H, m, 4"-H, 2 x alkene H); m/z (%) 323 (99, M^+), 322 (100); ν_{max} (KBr disc)/cm^{-1} 1634, 1612, 1560, 1533, 1433, 1375.

Example 100

(trans)-6,7-Dimethoxy-4-(4-phenylethenylanilino)quinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.10 g, 0.45 mmol) and 4-aminostilbene (TCI) (0.16 g, 0.82 mmol) were reacted in 2-propanol (15 ml) for 3 h according to Procedure B. The bright yellow solid thus obtained was 6,7-dimethoxy-4-(4-phenylethenylanilino)quinazoline hydrochloride (0.15 g, 80%), mp 264-265 °C; (Found: C, 68.39; H, 5.13; N, 9.88. $C_{24}H_{21}N_3O_2.HCl.0.1H_2O$ requires: C, 68.36; H, 5.31; N, 9.96%); δH [$^2H_6$]-DMSO 11.31 (1H, br s, NH), 8.80 (1H, s, 2-H), 8.32 (1H, s, 8-H), 7.78 (2H, d, J 8, 3'-H, 5'-H), 7.70 (2H, d, J 8, 2'-H, 6'-H), 7.62 (2H, d, J 8, 2"-H, 6"-H), 7.40-7.20 (6H, m, 5-H, 3"-H, 4"-H, 5"-H, 2 x alkene H), 4.03 (6H, 2 x s, 2 x OCH_3); m/z (%) 383 (100, M^+); ν_{max} (KBr disc)/cm^{-1} 1632, 1576, 1512, 1435, 1277.

Example 101

4-(4-Phenylethylanilino)quinazoline hydrochloride

A solution of 4-aminostilbene (TCI) (1.0 g, 5.13 mmol) in ethyl acetate (25 ml) was carefully added to 10% palladium on charcoal (0.050 g). The resulting suspension was stirred at r.t p. under an atmosphere of hydrogen. When the reaction was complete (ca. 30 min) (as indicated by tlc) the suspension was filtered through a pad of Hyflo, and the filtrate were evaporated to dryness to give 4-phenylethylaniline (0.77 g, 77%) as an off-white solid; δH [$^2H_6$]-DMSO 7.25 ((2H, t, J 8, 3'-H, 5'-H), 7.19 (2H, d, J 8, 2'-H, 6'-H), 7.16 (1H, t, J 8, 4'-H), 6.85 (2H, d, J 9, 3-H, 5-H), 6.48 (2H, d, J 9, 2-H, 6-H), 4.72 (2H, br s, NH_2), 2.78 (2H, m, CH_2), 2.70 (2H, m, CH_2). 4-Chloroquinazoline (0.10 g, 0.61 mmol) and 4-(phenylethyl)aniline (0.17 g, 0.85 mmol) were reacted in 2-propanol (6 ml) for 30 minutes according to Procedure B. The white solid thus obtained was 4-(4-phenylethylanilino)quinazoline hydrochloride (0.16 g, 73%), mp 263-264 °C; (Found: C, 73.14; H, 5.71; N, 11.50. $C_{22}H_{19}N_3.HCl$ requires: C, 73.02; H, 5.57; N, 11.61%); δH [$^2H_6$]-DMSO 11.55 (1H, br s, NH), 8.88 (1H, d, J 9, 8-H), 8.85 (1H, s, 2-H), 8.10 (1H, t, J 9, 6-H), 7.98 (1H, d, J 9, 5-H), 7.87 (1H, t, J 9, 7-H), 7.65 (2H, d, J 9, 2'-H, 6'-H), 7.35 (2H, t, J 9, 3'-H, 5'-H), 7.30-7.20 (4H, m, 2"-H, , 3"-H, 5"-H, 6"-H), 7.17 (1H, t, J 8, 4"-H), 2.95

(4H, s, CH_2CH_2); m/z (%) 325 (89, M^+), 234 (100); ν_{max} (KBr disc)/cm^{-1} 2617, 1634, 1616, 1595, 1566, 1543, 1431, 1377.

Example 102

6,7-Dimethoxy-4-(4-phenylethylanilino)quinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.10 g, 0.45 mmol) and 4-(phenylethyl)aniline (0.13 g, 0.67 mmol) were reacted in 2-propanol (15 ml) for 35 min according to Procedure B. The white solid thus obtained was 6,7-dimethoxy-4-(4-phenylethylanilino)quinazoline hydrochloride (0.14 g, 75%), mp 262-263 °C; (Found: C, 68.31; H, 5.78; N, 9.85. $C_{24}H_{23}N_3O_2.HCl$ requires: C, 68.32; H, 5.73; N, 9.96%); δH [$^2H_6$]-DMSO 11.20 (1H, br s, NH), 8.75 (1H, s, 2-H), 8.25 (1H, s, 8-H), 7.58 (2H, d, J 9, 2'-H, 6'-H), 7.40-7.20 (7H, m, 5-H, 3'-H, 5'-H, 2"-H, 3"-H, 5"-H, 6"-H), 7.17 (1H, t, J 8, 4"-H), 4.02 (6H, 2 x s, 2 x OCH_3), 2.95 (4H, s, CH_2CH_2); m/z (%) 385 (17, M^+), 294 (100); ν_{max} (KBr disc)/cm^{-1} 1634, 1574, 1516, 1435, 1362, 1281, 1230, 1063.

Example 103

4-(4-Phenylthioanilino)quinazoline hydrochloride

4-Chloroquinazoline (0.050 g, 0.30 mmol) and 4-(phenylthio)aniline (Salor) (0.070 g, 0.35 mmol) were reacted in 2-propanol (6 ml) for 15 minutes according to Procedure B. The bright yellow solid thus obtained was 4-(4-phenylthioanilino)quinazoline hydrochloride (0.075 g, 68%), mp 275-276 °C; (Found: C, 65.49; H, 4.43; N, 11.38. $C_{20}H_{15}N_3S.HCl$ requires: C, 65.65; H, 4.41; N, 11.48%); δH [$^2H_6$]-DMSO 11.60 (1H, br s, NH), 8.91 (1H, d, J 9, 8-H), 8.89 (1H, s, 2-H), 8.10 (1H, t, J 8, 6-H), 7.98 (1H, d, J 9, 5-H), 7.85 (1H, t, J 8, 7-H), 7.80 (2H, d, J 9, 2'-H, 6'-H), 7.45 (2H, t, J 9, 3'-H, 5'-H), 7.44-7.38 (4H, m, 2"-H, , 3"-H, 5"-H, 6"-H), 7.37 (1H, t, J 8, 4"-H); m/z (%) 329 (100, M^+); ν_{max} (KBr disc)/cm^{-1} 2538, 1630, 1612, 1566, 1537, 1495, 1433, 1375.

Example 104

4-(4-Phenylsulfonylanilino)quinazoline and 4-(4-phenylsulfinylanilino)quinazoline

Oxone® ($2KHSO_5.KHSO_4.K_2SO_4$) (0.13 g, 0.21 mmol) was added to a stirred suspension of 4-(4-phenylthioanilino)quinazoline hydrochloride (0.030 g, 0.082 mmol) in methanol (3 ml) and water (8 ml) at 0 °C and the mixture stirred for 3 h. The reaction mixture allowed to warm to room temperature and stirred for 10 h. Further Oxone® (0.025 g, 0.04 mmol) was added, since tlc indicated the presence of starting material, and the mixture stirred for a further 3 h.. The solvents were

removed in vacuo and the residue dissolved in water (8 ml). Saturated aq. sodium bicarbonate (5 ml) was added and the aqueous layer extracted with dichloromethane (3 x 5 ml). The combined extracts were evaporated in vacuo and the yellow residue chromatographed (silica gel, ethyl acetate) to give firstly 4-(4-phenylsulfonylanilino)-quinazoline (0.008 g, 28%) as a white solid, mp 231-232 °C; (Found: C, 65.43; H, 4.26, N, 11.02. $C_{20}H_{15}N_3O_2S$ 0.4 H_2O requires: C, 65.17; H, 4.32; N, 11.40%); δH [$^2H_6$]-DMSO 10.10 (1H, br s, NH), 8.70 (1H, s, 2-H), 8.58 (1H, d, J 9, 8-H), 8.20 (2H, d, J 9, 2'-H, 6'-H), 8.02-7.80 (6H, m, 5-H, 7-H, 3'-H, 5'-H, 2"-H, 6"-H), 7.70-7.55 (4H, m, 6-H, 3"-H, 4"-H, 5"-H); m/z (%) 361 (100, M^+); ν_{max} (KBr disc)/cm^{-1} 1566, 1516, 1408, 1391, 1149, 1105.

This was followed by 4-(4-phenylsulfinylanilino)quinazoline (0.002 g, 7%) as a white solid; δH [$^2H_6$]-DMSO 10.00 (1H, br s, NH), 8.62 (1H, s, 2-H), 8.55 (1H, d, J 9, 8-H), 8.06 (2H, d, J 9, 2'-H, 6'-H),, 7.92-7.48 (10H, m, 5-H, 6-H, 7-H, 3'-H, 5'-H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H); m/z (%) 345 (12, M^+), 329 (100).

Example 105

6,7-Dimethoxy-4-(4-phenylthioanilino)quinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.10 g, 0.45 mmol) and 4-(phenylthio)aniline (Salor) (0.13 g, 0.62 mmol) were reacted in 2-propanol (15 ml) for 45 min according to Procedure B. The pale yellow solid thus obtained was 6,7-dimethoxy-4-(4-phenylthioanilino)quinazoline hydrochloride (0.16 g, 82%), mp 257-258 °C; (Found: C, 61.87; H, 4.69; N, 9.71. $C_{22}H_{19}N_3O_2S.HCl$ requires: C, 62.04; H, 4.73; N, 9.87%); δH [$^2H_6$]-DMSO 11.35 (1H, br s, NH), 8.80 (1H, s, 2-H), 8.33 (1H, s, 8-H), 7.77 (2H, d, J 9, 2'-H, 6'-H), 7.45 (2H, d, J 9, 3'-H, 5'-H), 7.40-7.30 (6H, m, 5-H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H), 4.01 (6H, 2 x s, 2 x CH_3); m/z (%) 389 (100, M^+); ν_{max} (KBr disc)/cm^{-1} 2700, 1632, 1578, 1514, 1439, 1364, 1281, 1232.

Example 106

6,7-Dimethoxy-4-(4-phenylsulfonylanilino)quinazoline and 6,7-dimethoxy-4-(4-phenylsulfinylanilino)quinazoline

Oxone® ($2KHSO_5.KHSO_4.K_2SO_4$) (0.075 g, 0.12 mmol) was added to a stirred suspension of 6,7-dimethoxy-4-(4-phenylthioanilino)quinazoline hydrochloride (0.050 g, 0.12 mmol) in methanol (3 ml) and water (3 ml) at 0 °C and the mixture stirred for 2 h. The reaction mixture was then allowed to warm to room temperature and stirred for 10 h. The solvents were removed in vacuo and the residue treated with dichloromethane (2 ml) and methanol (1 ml) to give a white suspension. This was filtered and the solids washed with methanol (5 ml). The filtrate was treated

with triethyamine (2.5 ml), concentrated in vacuo, and the residue chromatographed (silica gel, ethyl acetate) to give firstly 6,7-dimethoxy-4-(4-phenylsulfonylanilino)quinazoline (0.003 g, 6%) as an off-white solid, mp 223-226°C; δH [$^2H_6$]-DMSO 9.72 (1H, br s, NH), 8.55 (1H, s, 2-H), 8.12 (2H, d, J 9, 2'-H, 6'-H), 7.92-7.98 (4H, 2 x d, 3'-H, 5'-H, 2"-H, 6"-H), 7.85 (1H, s, 8-H), 7.60-7.70 (3H, m, 3"-H, 4"-H, 5"-H), 7.23 (1H, s, 5-H), 3.97 (6H, 2 x s, 2 x OCH_3); m/z (%) 422 (100, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1622, 1595, 1576, 1502, 1410, 1246, 1151, 1107.

This was followed by 6,7-dimethoxy-4-(4-phenylsulfinylanilino)quinazoline (0.002 g, 4%) as a beige solid, mp 227 °C (dec); δH [$^2H_6$]-DMSO 9.90 (1H, br s, NH), 8.55 (1H, s, 2-H), 7.97 (2H, d, J 9, 2'-H, 6'-H), 7.87 (1H, s, 8-H), 7.72-7.70 (4H, m, 3'-H, 5'-H, 2"-H, 6"-H), 7.50-7.58 (3H, m, 3"-H, 4"-H, 5"-H), 7.20 (1H, s, 5-H), 3.97 (6H, 2 x s, 2 x OCH_3); m/z (%) 406 (100, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1626, 1576, 1506, 1119, 1242, 1030.

Example 107

4-[4-(Benzylthio)anilino]quinazoline hydrochloride

Potassium carbonate (4.0 g, .0.029 mol) was added to a solution of nitrothiophenol (Aldrich) (2.7 g, 0.017 mol) in acetone (40 ml). Benzyl bromide (3 ml, 0.025 mol) was then added at r.t. over a period of 1 min, during which the colour changed gradually from red to orange. The mixture was then stirred for 10 min, the acetone was evaporated and the residue partitioned between dichloromethane (50 ml) and water (50 ml). The organic layer was separated, dried (Na_2SO_4), evaporated and the residue chromatographed (silica gel, 20% dichloromethane/40-60 petrol) to give 4-(benzylthio)nitrobenzene (1.7, 41%) as a pale yellow solid; δH [$^2H_6$]-DMSO 8.12 (2H, d, J 9, 2-H, 6-H), 7.56 (2H, d, J 9, 3-H, 5-H), 7.45 (2H, d, J 9, 2'-H, 6'-H), 7.35 (2H, t, J 9, 3'-H, 5'-H), 7.28 (1H, t, J 9, 4'-H), 4.42 (2H, s, CH_2).

A solution of 4-(benzylthio)nitrobenzene (1.0 g, 4.1 mmol) in methanol (100 ml) was carefully added to 10% palladium on charcoal (0.5 g). The resulting suspension was stirred at room temperature and pressure under an atmosphere of hydrogen. When the reaction was complete (ca. 3 h) (as indicated by tlc) the suspension was filtered through a pad of Hyflo. The filtrate was then evaporated to dryness and the residue chromatographed (silica gel, 30% diethyl ether/40-60 petrol) to give 4-(benzylthio)aniline (0.71 g, 80%) as a colourless oil; δH [$^2H_6$]-DMSO 7.38-7.15 (2'-H. 3'-H, 4'-H, 5'-H, 6'-H), 7.02 (2H, d, J 9, 3-H, 5-H), 6.50 (2H, d, J 9, 2-H, 6-H), 5.15 (2H, br s, NH_2), 3.92 (2H, s, CH_2).

4-Chloroquinazoline (0.10 g, 0.61 mmol) and 4-benzylthioaniline (0.17 g, 0.79 mmol) were reacted in 2-propanol (6 ml) for 30 minutes according to Procedure B except that the reaction was stirred at room temperature. The bright yellow solid thus obtained was 4-[4-(benzylthio)anilino]quinazoline hydrochloride (0.18 g, 80%), mp 215-216 °C; (Found: C, 66.64; H, 4.80; N, 10.93. $C_{21}H_{17}N_3S.HCl$ requires: C, 66.39; H, 4.78; N, 11.06%); δH [$^2H_6$]-DMSO 11.60 (1H, br s, NH), 8.90 (1H, d, J 9, 8-H), 8.88 (1H, s, 2-H), 8.09 (1H, t, J 8, 6-H), 7.98 (1H, d, J 8, 5-H), 7.85 (1H, t, J 8, 7-H), 7.70 (2H, d, J 9, 2'-H, 6'-H), 7.44 (2H, t, J 9, 3'-H, 5'-H), 7.38 (2H, d, J 8, 2"-H, 6"-H), 7.30 (2H, t, J 8, 3"-H, 5"-H), 7.22 (1H, t, J 8, 4"-H), 4.28 (2H, s, SCH_2); m/z (%) 343 (62, M^+), 252 (100); ν_{max} (KBr disc)/cm^{-1} 2636, 1634, 1612, 1566, 1537, 1495, 1429, 1375.

Example 108

4-[4-(Benzylthio)anilino]-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.10 g, 0.45 mmol) and 4-benzylthioaniline (0.15 g, 0.67 mmol) were reacted in 2-propanol (15 ml) for 35 min according to Procedure B. The pale yellow solid thus obtained was 4-[4-(benzylthio)anilino]-6,7-dimethoxyquinazoline hydrochloride (0.19 g, 97%), mp 242-244 °C; (Found: C, 62.80; H, 5.01; N, 9.42. $C_{23}H_{21}N_3O_2S.HCl$ requires: C, 62.79; H, 5.04; N, 9.55%); δH [$^2H_6$]-DMSO 11.40 (1H, br s, NH), 8.80 (1H, s, 2-H), 8.37 (1H, s, 8-H), 7.68 (2H, d, J 9, 2'-H, 6'-H), 7.44 (2H, d, J 9, 3'-H, 5'-H), 7.40 (1H, s, 5-H), 7.39 (2H, d, J 9, 2"-H, 6"-H), 7.30 (2H, t, J 9, 3"-H, 5"-H), 7.25 (1H, t, J 9, 4"-H), 4.28 (2H, s, SCH_2), 4.01 (6H, 2 x s, 2 x OCH_3); m/z (%) 403 (55, M^+), 312 (100); ν_{max} (KBr disc)/cm^{-1} 1634, 1587, 1574, 1516, 1435, 1281, 1063.

Example 109

4-(4-Benzylsulfonylanilino)-6,7-dimethoxy-quinazoline

A two phase mixture of 4-[4-(benzylthio)anilino]-6,7-dimethoxyquinazoline hydrochloride (0.070 g, 0.16 mmol) in dichloromethane (3 ml) and sat. aq. sodium bicarbonate (3 ml) was stirred and cooled to 0 °C, and then treated with 85% m-chloroperbenzoic acid (0.082g, 0.48 mmol). The reaction mixture was stirred for 1 h, warmed to room temperature and the mixture stirred for a further 1 h. The organic and aqueous layers were separated and the aqueous layer extracted with dichloromethane (4 x 5 ml). The combined extracts were dried (Na_2SO_4) and evaporated to dryness. Chromatography (silica gel, ethyl acetate) gave 4-(4-benzylsulfonylanilino)-6,7-dimethoxyquinazoline (0.012 g, 17%) as an off-white solid, mp 249-250 °C; (Found: C, 60.39; H, 4.91; N, 9.05. $C_{23}H_{21}N_3O_4S.1.1H_2O$

requires: C, 60.68; H, 5.14; N, 9.23%); δH [$^2H_6$]-DMSO 9.70 (1H, br s, NH), 8.58 (1H, s, 2-H), 8.08 (2H, d, J 9, 3'-H, 5'-H), 7.86 (1H, s, 8-H), 7.67 (2H, d, J 9, 2'-H, 6'-H), 7.35-7.25 (3H, m, 3"-H, 4"-H, 5"-H), 7.24 (1H, s, 5-H), 7.18 (2H, d, J 8, 2"-H, 6"-H), 4.61 (2H, s, SO_2CH_2), 4.01 (6H, 2 x s, 2 x OCH_3); m/z (%) 435 (35, M^+), 371 (28), 280 (29), 91 (100); ν_{max} (KBr disc)/cm^{-1} 1628, 1597, 1576, 1419, 1399, 1244, 1144.

Example 110

4-(4-Phenylthiomethylanilino)quinazoline hydrochloride

4-Nitrobenzylbromide (Aldrich) (5.0 g, 0.023 mol), thiophenol (2.4 ml, 0.023 mol) and potassium carbonate (3.84 g, 0.28 mol) were mixed with acetone (200 ml) and heated at reflux for 3 h. Potassium iodide (ca. 0.100 g) was then added and the whole heated at reflux for a further 2 h. The mixture was then cooled and passed thrugh a short pad of silica gel. The filtrate was evaporated and the residue chromatographed (silica gel, gradient elution, 40-60 petrol through to 30% diethyl ether/40-60 petrol) to give 4-phenylthiomethylnitrobenzene (4.0 g, 71%) as a white solid; δH [$^2H_6$]-DMSO 8.13 (2H, d, J 9, 2-H, 6-H), 7.59 (2H, d, J 9, 3-H, 5-H), 7.34 (2H, d, J 8, 2'-H, 6'-H), 7.29 (2H, t, J 8, 3'-H, 5'-H), 7.20 (1H, t, J 8, 4'-H), 4.37 (2H, s, CH_2S).

A solution of 4-phenylthiomethylnitrobenzene (0.50 g, 2.0 mmol) in methanol (25 ml) was carefully added to 10% palladium on charcoal (0.17 g). The resulting suspension was stirred at r.t p. for 2 h under an atmosphere of hydrogen. Due to the insolubility of the substrate, ethyl acetate (20 ml) was added along with a suspension of 10% palladium on charcoal (0.050 g) in ethyl acetate and the mixture stirred under hydrogen for 5 h. A further suspension of 10% palladium on charcoal (0.050 g) in ethyl acetate was added and the reaction continued. When the reaction was complete (ca. 16 h) (as indicated by tlc) the suspension was filtered through a pad of Hyflo. The filtrate was then evaporated to dryness and the residue chromatographed (silica gel, 30% diethyl ether/40-60 petrol) to give 4-phenylthiomethylaniline (0.26 g, 60%) as a white solid; δH [$^2H_6$]-DMSO 7.32-7.25 (4H, m, 2'-H. 3'-H, 5'-H, 6'-H), 7.17 (1H, t, J 8, 4'-H), 6.98 (2H, d, J 9, 3-H, 5-H), 6.48 (2H, d, J 9, 2-H, 6-H), 4.94 (2H, br s, NH_2), 4.05 (2H, s, CH_2S).

4-Chloroquinazoline (0.075 g, 0.46 mmol) and 4-phenylthiomethylaniline (0.16 g, 0.55 mmol) were reacted in 2-propanol (6 ml) for 15 minutes according to Procedure B. The pale yellow solid thus obtained was 4-(4-phenylthiomethylanilino)quinazoline hydrochloride (0.15 g, 84%), mp 257-259 °C; (Found: C, 66.37; H, 4.80; N, 10.94. $C_{21}H_{17}N_3S.HCl$ requires: C, 66.39; H, 4.78;

N, 11.06%); δH [$^2H_6$]-DMSO 11.85 (1H, br s, NH), 9.02 (1H, d, J 8, 8-H), 8.88 (1H, s, 2-H), 8.10 (1H, t, J 8, 6-H), 8.03 (1H, d, J 8, 5-H), 7.85 (1H, t, J 8, 7-H), 7.70 (2H, d, J 9, 2'-H, 6'-H), 7.45 (2H, t, J 9, 3'-H, 5'-H), 7.37 (2H, d, J 9, 2"-H, 6"-H), 7.31 (2H, t, J 9, 3"-H, 5"-H), 7.20 (1H, t, J 9, 4"-H), 4.30 (2H, s, SCH_2); m/z (%) 344 (100, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 2631, 1628, 1612, 1560, 1537, 1425, 1375.

Example 111

6,7-Dimethoxy-4-(4-phenylthiomethylanilino)quinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.10 g, 0.45 mmol) and 4-phenylthiomethylaniline (0.12 g, 0.63 mmol) were reacted in 2-propanol (15 ml) for 15 min according to Procedure B. The white solid thus obtained was 6,7-dimethoxy-4-[4-phenylthiomethylanilino]quinazoline hydrochloride (0.12 g, 65%), mp 235-236 °C; (Found: C, 62.64; H, 5.04; N, 9.57. $C_{23}H_{21}N_3O_2S.HCl$ requires: C, 62.79; H, 5.04; N, 9.55%); δH [$^2H_6$]-DMSO 11.40 (1H, br s, NH), 8.78 (1H, s, 2-H), 8.35 (1H, s, 8-H), 7.65 (2H, d, J 9, 2'-H, 6'-H), 7.45 (2H, d, J 9, 3'-H, 5'-H), 7.40-7.35 (3H, m, 5-H, 2"-H, 6"-H), 7.32 (2H, t, J 9, 3"-H, 5"-H), 7.20 (1H, t, J 9, 4"-H), 4.30 (2H, s, SCH_2), 4.00 (6H, 2 x s, 2 x OCH_3); m/z (%) 404 (100, $M+1^+$); ν_{max} (KBr disc)/cm^{-1} 1632, 1578, 1514, 1437, 1281, 1067.

Example 112

6,7-Dimethoxy-4-[4-(phenylsulfonylmethyl)anilino]quinazoline

Oxone® ($2KHSO_5.KHSO_4.K_2SO_4$) (0.11 g, 0.17 mmol) was added to a stirred suspension of 6,7-dimethoxy-4-[4-(phenylthiomethyl)anilino]quinazoline hydrochloride (0.050 g, 0.11 mmol) in methanol (5 ml) and water (5 ml) at 30 °C and the mixture stirred for 1 h. The reaction mixture was then gradually warmed to 60 °C over 5 h and stirred at that temperature for 2 h. Stirring was continued at room temperature for 10 h. Further Oxone® (0.005 g, 0.008 mmol) was added (since tlc indicated the presence of sulphoxide intermediate) and the mixture was stirred at 60 °C for a further 2 h.. The solution was treated with saturated aq. sodium bicarbonate (11 ml) and extracted with dichloromethane (3 x 5 ml). The combined extracts were evaporated in vacuo and the yellow residue chromatographed (silica gel, ethyl acetate) to give 6,7-dimethoxy-4-[4-(phenylsulfonylmethyl)anilino]-quinazoline (0.008 g, 16%) as an orange solid, mp 255 °C (dec); δH [$^2H_6$]-DMSO 9.47 (1H, br s, NH), 8.45 (1H, s, 2-H), 7.82 (1H, s, 8-H), 7.78-7.70 (5H, m, 2'-H, 6'-H, 2"-H, 4"-H, 6"-H), 7.63 (2H, t, J 9, 3"-H, 5"-H), 7.20 (1H, s, 5-H), 7.15 (2H, d, J 9, 3'-H, 5'-H), 4.65 (2H, s, CH_2SO_2), 3.95 (6H, 2 x

s, 2 x OCH_3); m/z (%) 435 (4, M^+), 294 (100); ν_{max} (KBr disc)/cm^{-1} 1622, 1576, 1514, 1421, 1242, 1153, 1130.

Example 113

4-(4-Phenoxymethylanilino)quinazoline

A mixture of 4-nitrobenzylbromide (Aldrich) (5.0 g, 0.023 mol), phenol (2.2, 0.023 mol) and potassium carbonate (3.5 g, 0.025 mol) in acetone (100 ml) was heated at reflux. After 1 h further phenol (2.2 g, 0.023 mol) and potassium carbonate (3.5 g, 0.025 mol) were added and the reaction heated at reflux for a further 30 min. The solvents were then removed in vacuo and the remaining oil subjected to dry flash chromatography (silica gel, 30% dichloromethane/petrol) to give 4-phenoxymethylnitrobenzene (4.2 g, 80%) as a white crystalline solid; δH [$^2H_6$]-DMSO 8.25 (2H, d, J 9, 2-H, 6-H), 7.73 (2H, d, J 9, 3-H, 5-H), 7.30 (2H, t, J 9, 3'-H, 5'-H), 7.04 (2H, d, J 9, 2'-H, 6'-H), 6.98 (1H, t, J 8, 4'-H), 5.27 (2H, s, CH_2O).

Methanol (30 ml) was carefully added to 4-phenoxymethylnitrobenzene (1.0 g, 4.1 mmol) and platinum (IV) oxide (0.050 g, 0.22 mmol). The resulting suspension was stirred at r.t p. under an atmosphere of hydrogen. When the reaction was complete (ca. 80 min) (as indicated by tlc) the suspension was diluted with dichloromethane (30 ml) and filtered through a pad of Hyflo. The filtrate was then evaporated to give 4-phenoxymethylaniline (0.71 g, 80%) as a white solid; δH $CDCl_3$ 7.25 (2H, t, J 9, 3'-H, 5'-H), 7.21 (2H, d, J 9, 2'-H, 6'-H), 6.98 (2H, d, J 9, 3-H, 5-H), 6.92 (1H, t, J 9, 4'-H), 6.69 (2H, d, J 9, 2-H, 6-H), 4.92 (2H, s, CH_2O), 3.65 (2H, br s, NH_2).

4-Chloroquinazoline (0.10 g, 0.61 mmol) and 4-phenoxymethylaniline (0.15 g, 0.73 mmol) were reacted in 2-propanol (6 ml) for 20 min according to Procedure B. The resulting bright yellow solid was suspended in dichloromethane, treated with triethylamine and the whole stirred at room temperature for 5 min. The volatiles were then removed in vacuo, and the residue chromatographed twice on silica gel (firstly using 2% methanol/dichloromethane; secondly, 40% petrol/diethyl ether) to give 4-(4-phenoxymethylanilino)quinazoline (0.010 g, 5%), mp 194-195 °C; (Found: C, 76.64; H, 5.35; N, 12.71. $C_{21}H_{17}N_3O.0.1H_2O$ requires: C, 76.62; H, 5.27; N, 12.76%); δH [$^2H_6$]-DMSO 9.77(1H, s, NH), 8.61 (1H, s, 2-H), 8.55 (1H, d, J 9, 8-H), 7.88 (2H, d, J 9, 2'-H, 6'-H), 7.87 (1H, t, J 8, 6-H), 7.80 (1H, d, J 8, 5-H), 7.65 (1H, t, J 8, 7-H), 7.47 (2H, t, J 9, 3'-H, 5'-H), 7.30 (2H, t, J 9, 3"-H, 5"-H), 7.03 (2H, d, J 9, 2"-H, 6"-H), 6.95 (1H, t, J 8, 4"-H), 5.10 (2H, s, OCH_2); m/z (%) 327 (2, M^+), 234 (100); ν_{max} (KBr disc)/cm^{-1} 1618, 1599, 1572, 1528, 1499, 1419, 1238, 756.

Example 114

6,7-Dimethoxy-4-(4-phenoxymethylanilino)quinazoline

A stirred mixture of 4-chloro-6,7-dimethoxyquinazoline (0.11 g, 0.50 mmol) and 4-phenoxymethylaniline (0.14 g, 0.70 mmol) was heated to reflux in 2-propanol (6 ml) for 1 h. After cooling, triethylamine was added to the mixture was stirred at room temperature for 5 min. The volatiles were then removed in vacuo and the residue chromatographed (silica gel, 5% methanol/dichloromethane) to give 6,7-dimethoxy-4-(4-phenoxymethylanilino)quinazoline (0.020 g, 10%), mp 250 °C (dec); (Found: C, 71.55; H, 5.58; N, 10.76. $C_{23}H_{21}N_3O_3$ requires: C, 71.30; H, 5.46; N, 10.85%); δH [$^2H_6$]-DMSO 9.45 (1H, br s, NH), 8.45 (1H, s, 2-H), 7.86 (1H, s, 8-H), 7.83 (2H, d, J 9, 2'-H, 6'-H), 7.47 (2H, d, J 9, 3'-H, 5'-H), 7.30 (2H, t, J 8, 3"-H, 5"-H), 7.20 (1H, s, 5-H), 7.03 (2H, d, J 8, 2"-H, 6"-H), 6.95 (1H, t, J 9, 4"-H), 5.10 (2H, s, CH_2O), 3.95 (6H, 2 x s, 2 x OCH_3); m/z (%) 387 (13, M^+), 294 (100); ν_{max} (KBr disc)/cm^{-1} 1622, 1597, 1578, 1518, 1473, 1423, 1240.

Example 115

4-(4-Benzyloxy-2-methylanilino)quinazoline

3-Methyl-4-nitrophenol (Aldrich) (2.50 g; 16.3 mmol), sodium hydride (0.405 g; 16.4 mmol) and benzyl chloride (2.28 g; 17.0 mmol) were reacted in dimethylformamide (100 ml) at 60°C for 5 hours according to Procedure E. 5-Benzyloxy-2-nitrotoluene was thus obtained as a beige solid (3.2 g, 88%) with mp 64-66°C; (Found, C, 68.77; H, 5.40; N, 5.74. $C_{14}H_{13}NO_3$ requires C, 69.14; H, 5.35; N, 5.76); tlc (dichloromethane) Rf 0.78.

5-Benzyloxy-2-nitrotoluene (0.500 g; 2.06 mmol) was reduced with hydrazine hydrate (0.308 g; 6.17 mmol) according to Procedure H to give 4-benzyloxy-2-methylaniline (0.430 g, 98%) as a colourless oil; tlc (ethyl acetate) Rf 0.55.

4-Chloroquinazoline (0.326 g; 1.98 mmol) and 4-benzyloxy-2-methylaniline (0.430 g; 2.02 mmol) were reacted in 2-propanol (18 ml) for 70 minutes according to Procedure C. 4-(4-Benzyloxy-2-methylanilino)quinazoline was thus obtained as a yellow solid (0.354 g, 52%) with mp 176-178°C; (Found C, 76.46; H, 5.46; N, 12.04. $C_{22}H_{19}N_3O.0.25H_2O$ requires C, 76.41; H, 5.64; N, 12.16); tlc (methanol:dichloromethane, 3:47) Rf 0.40; δH [$^2H_6$]-DMSO 10.98 (1H, br s, NH), 8.69 (1H, s, 2-H), 7.71-7.94 (3H, m, 5-H, 7-H, 8-H), 7.35-7.58 (5H, m, 6-H, 6'-H, 3 x PhH), 7.31 (1H, s, PhH), 7.18 (1H, s, PhH), 6.88-7.00 (2H, m, 3'-H, 5'-H), 5.10 (2H, s, CH_2), 2.35 (3H, s, 2'-CH_3); m/z (%) 342 (100, $M+1^+$).

Example 116

4-(4-Benzyloxy-2-methylanilino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.420 g; 1.87 mmol) and 4-benzyloxy-2-methylaniline (0.439 g; 2.06 mmol) were reacted in 2-propanol (15 ml) for 30 minutes acording to Procedure B. The product was thus obtained as a pale beige solid (0.652 g, 74%) with mp 226-228°C; (Found C, 61.36; H, 5.63; N, 8.99. $C_{24}H_{23}N_3O_3.1.5HCl.0.75H_2O$ requires C, 61.37;. H, 5.54; N, 8.96); tlc (ethyl acetate) Rf 0.15; δH [$^2H_6$]-DMSO 10.86 (1H, br s, NH), 8.60 (1H, s, 2-H), 8.20 (1H, s, 8-H), 6.88-7.52 (9H, m, 5-H, 3'-H, 5'-H, 6'-H, 5 x PhH), 5.18 (2H, s, CH_2), 3.98 (6H, s, 2 x OCH_3), 2.18 (3H, s, 2'-CH_3); m/z (%) 401 (26, M+), 310 (100).

Example 117

4-(4-Benzyloxy-3-chloroanilino)quinazoline hydrochloride

2-Chloro-4-nitrophenol (Lancaster) (5.0 g; 28.8 mmol), sodium hydride (0.784 g; 31.7 mmol) and benzyl bromide (5.42 g; 31.7 mmol) were reacted in dimethylformamide (70 ml) at 55°C for 5 hours according to Procedure E. 4-Benzyloxy-3-chloronitrobenzene was thus obtained as a dull yellow powder (6.9 g, 91%) with mp 111-113°C; (Found C, 59.20; H, 3.74; N, 5.22. $C_{13}H_{10}ClNO_3$ requires C, 59.20; H, 3.80; N, 5.31); tlc (dichloromethane) Rf 0.67.

4-Benzyloxy-3-chloronitrobenzene (0.500 g; 1.90 mmol) was reduced with hydrazine hydrate (0.284 g; 5.68 mmol) according to the Procedure H. 4-Benzyloxy-3-chloroaniline (0.440 g, 99%) was obtained as a colourless solid with mp 83-84°C; tlc (ethyl acetate:cyclohexane, 1:1) Rf 0.61.

4-Chloroquinazoline (0.258 g; 1.57 mmol) and 4-benzyloxy-3-chloroaniline (0.440 g; 1.90 mmol) were reacted in 2-propanol (14 ml) for 30 minutes according to Procedure B. The product was thus obtained as a yellow solid (0.532 g, 85%) with mp 222-224°C; (Found C, 63.04; H, 4.42; N, 10.41. $C_{21}H_{16}ClN_3O.HCl$ requires C, 63.31; H, 4.27; N, 10.55); tlc (ethyl acetate) Rf 0.43; δH [$^2H_6$]-DMSO 11.82 (1H, br s, NH), 9.00 (1H, d, J 7, 8-H), 8.95 (1H, s, 2-H), 7.64-8.14 (5H, m, 5-H, 6-H, 7-H, 2'-H, 6'-H), 7.22-7.54 (6H, m, 5'-H, 5 x PhH), 5.30 (2H, s, CH_2); m/z (%) 362 (100, $M+1^+$).

Example 118

4-(4-Benzyloxy-3-chloroanilino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.353 g; 1.57 mmol) and 4-benzyloxy-3-chloroaniline (0.440 g; 1.90 mmol) were reacted in 2-propanol (20 ml) for 20 minutes according to Procedure B. The product was thus obtained as a beige solid (0.646 g, 90%) with mp 256-258°C; (Found C, 60.13; H, 4.59; N, 9.12. $C_{23}H_{20}ClN_3O_3.HCl$ requires C, 60.26; H, 4.59; N, 9.17); tlc (ethyl acetate) Rf 0.22; δH [$^2H_6$]-DMSO 11.35

(1H, br s, NH), 8.79 (1H, s, 2-H), 8.37 (1H, s, 8-H), 7.90 (1H, s, 7-H), 7.21-7.70 (8H, m, 2'-H, 5'-H, 6'-H, 5 x PhH), 5.30 (2H, s, CH_2), 4.07 and 4.01 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 422 (90, $M+1^+$), 331 (50).

Example 119

4-(4-Benzyloxy-3-chloroanilino)-6-bromoquinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.139 g; 0.571 mmol) and 4-benzyloxy-3-chloroaniline (0.146 g; 0.628 mmol) were reacted in 2-propanol (8 ml) for 4.5 hours according to Procedure B. The product was thus obtained as a bright yellow solid (0.255 g, 94%) with mp 256-258°C; (Found C, 52.78; H, 3.44; N, 8.66. $C_{21}H_{15}BrClN_3O.HCl$ requires C, 52.84; H, 3.36; N, 8.81); tlc (ethyl acetate) Rf 0.51; δH [$^2H_6$]-DMSO 11.26 (1H, br s, NH), 9.11 (1H, s, 5-H), 8.90 (1H, s, 2-H), 8.20 (1H, d, J 9, 7-H), 7.95 (1H, s, 2'-H), 7.87 (2H, d, J 9, 6'-H, 8-H), 7.70 (2H, d, J 9, 2"-H, 6"-H), 7.29-7.55 (4H, m, 5'-H, 3"-H, 4"-H, 5"-H), 5.29 (2H, s, CH_2); m/z 441 (26, M+), 350 (100).

Example 120

4-(4-Benzyloxy-3-methoxyanilino)-6,7-dimethoxyquinazoline hydrochloride

2-Methoxy-4-nitrophenol (Aldrich) (2.53 g; 15.0 mmol), sodium hydride (0.400 g; 16.5 mmol) and benzyl bromide (2.62 g; 16.0 mmol) were reacted in dimethylformamide (50 ml) at 55°C for 6.5 hours according to Procedure E. 4-Benzyloxy-3-methoxynitrobenzene was thus obtained as a pale yellow solid (3.05 g, 79%) with mp 78-79°C; (Found C, 64.95; H, 5.01; N, 5.39. $C_{14}H_{13}NO_4$ requires C, 64.86; H, 5.02; N,5.40); tlc (dichloromethane) Rf 0.81.

4-Benzyloxy-3-methoxynitrobenzene (1.17 g; 4.52 mmol) was reduced with hydrazine hydrate (0.678 g; 13.56 mmol) according to Procedure H. 4-Benzyloxy-3-methoxyaniline (1.03 g, 98%) was obtained as colourless needles with mp 62-63°C; tlc (dichloromethane) Rf 0.62.

4-Chloro-6,7-dimethoxyquinazoline (0.225 g; 1.0 mmol) and 4-benzyloxy-3-methoxyaniline (0.276 g; 1.25 mmol) were reacted in 2-propanol (7.5 ml) for 45 minutes according to Procedure B. The product was thus obtained as a yellow crystalline solid (0.420 g, 93%) with mp 251-252°C; (Found C, 62.91; H, 5.18; N, 9.12. $C_{24}H_{23}N_3O_4.HCl.0.25H_2O$ requires C, 62.88; H, 5.34; N, 9.17); tlc (ethyl acetate) Rf 0.18; δH [$^2H_6$]-DMSO 11.34 (1H, br s, NH), 8.78 (1H, s, 2-H), 8.35 (1H, s, 8-H), 7.05-7.51 (9H, m, 5-H, 2'-H, 5'-H, 6'-H, 5 x PhH), 5.12 (2H, s, CH_2), 4.02 and 4.00 (2 x 3H, 2 x s, 6-OCH_3, 7-OCH_3), 3.82 (3H, s, 3'-OCH_3); m/z 417 (15, M+), 326 (100).

Example 121

4-(4-Benzyloxy-2-nitroanilino)quinazoline hydrochloride

4-Chloroquinazoline (0.164 g; 1.0 mmol) and 4-benzyloxy-2-nitroaniline (Salor *via* Aldrich) (0.286 g; 1.1 mmol) were reacted in 2-propanol (5 ml) for 1.5 hours according to Procedure B. The product was thus obtained as a bright yellow crystalline solid (0.270 g, 66%) with mp 225-226°C; (Found C, 62.05; H, 4.07; N, 13.84. $C_{21}H_{16}N_4O_3$.HCl requires C, 61.69; H, 4.16; N, 13.70); tlc (ethyl acetate), Rf 0.38; δ H[$^2H_6$]-DMSO 12.22 (1H, br, s, NH), 8.92 (2H, d, J 9, 8-H, 5-H), 8.88 (1H, s, 2-H), 7.30-8.17 (10H, m, 6-H, 7-H, 3'-H, 5'-H, 6'-H, 5 x PhH), 5.31 (2H, s, CH_2); m/z (%) 372 (13, M+), 326 (36), 281 (16).

Example 122

4-(4-Benzyloxy-2-nitroanilino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.225 g; 1.0 mmol) and 4-benzyloxy-2-nitroaniline (0.268 g; 1.1 mmol) were reacted in 2-propanol (5 ml) for 4.5 hours according to Procedure B. The product was thus obtained as a bright yellow solid (0.350 g, 75%) with mp 249-251°C; (Found C, 59.45; H, 4.33; N, 11.99. $C_{23}H_{20}N_4O_5$.HCl requires C, 58.91; H, 4.48; N, 11.95); tlc (ethyl acetate) Rf 0.38; δH[$^2H_6$]-DMSO 11.86 (1H, br s, NH), 8.71 (1H, s, 2-H), 8.36 (1H, s, 8-H), 7.35-7.80 (9H, m, 7-H, 3'-H, 5'-H, 6'-H, 5 x PhH), 5.30 (2H, s, CH_2), 4.03 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 432 (30, M+), 386 (70), 341 (66).

Example 123

4-(4-Benzyloxy-3,5-dibromoanilino)quinazoline hydrochloride

2,6-Dibromo-4-nitrophenol (Aldrich) (2.0 g; 6.75 mmol), benzyl alcohol (0.873 g; 8.08 mmol) and dicyclohexylcarbodiimide (1.53 g; 7.41 mmol) were reacted for 12 hours according to Procedure G. 4-Benzyloxy-3,5-dibromonitrobenzene was thus obtained as colourless needles (1.55 g, 60%) with mp 82-84°C; (Found C, 40.80; H, 2.34; N, 3.50. $C_{13}H_9Br_2NO_3$ requires C, 40.33; H, 2.33; N, 3.62); tlc (dichloromethane-hexane, 1:1) Rf 0.35.

4-Benzyloxy-3,5-dibromonitrobenzene (0.200 g; 0.517 mmol) was reduced with hydrazine hydrate (0.078 g; 1.55 mmol) according to Procedure H. 4-Benzyloxy-3,5-dibromoaniline (0.179 g, 97%) was obtained as off-white plates with mp 93-94°C; tlc (ethyl acetate-cyclohexane, 1:1) Rf 0.61.

4-Chloroquinazoline (0.079 g; 0.48 mmol) and 4-benzyloxy-3,5-dibromoaniline (0.184 g; 0.317 mmol) were reacted in 2-propanol (5 ml) for 3 hours according to Procedure B. The product was thus obtained as a pale yellow solid (0.168 g, 67%) with mp 238-240°C; (Found C, 48.66; H, 3.08; N, 8.11. $C_{21}H_{15}Br_2N_3O$.HCl requires C, 48.34; H,

3.07; N, 8.06); tlc (ethyl acetate) Rf 0.22; δH[$^2H_6$]-DMSO 11.40 (1H, br s, NH), 8.98 (1H, s, 2-H), 8.81 (1H, d, J 7, 8-H), 8.20 (2H, s, 2'-H, 6'-H), 7.73-8.11 (4H, m, 6-H, 7-H, 2 x PhH), 7.55 (1H, d, J 9, 5-H), 7.24-7.48 (3H, m, 3 x PhH), 5.04 (2H, s, CH_2); m/z (%) 485 (15, M+), 404, 406 (24), 394 (78).

Example 124

4-(4-Benzyloxy-3,5-dibromoanilino)-6,7-dimethoxyquinazoline

4-Chloro-6,7-dimethoxyquinazoline (0.108 g; 0.481 mmol) and 4-benzyloxy-3,5-dibromoaniline (0.184 g; 0.517 mmol) were reacted in 2-propanol (6 ml) for 2.5 hours according to Procedure C. The product was thus obtained as a colourless solid (0.050 g, 19%) with mp 137-140°C; (Found C, 49.13; H, 3.73; N, 7.44. $C_{23}H_{19}Br_2N_3O_3.H_2O$ requires C, 49.04; H, 3.73; N, 7.46); tlc (methanol:dichloromethane, 7:93); Rf 0.45; δH [$^2H_6$]-DMSO 11.06 (1H, br s, NH), 8.71 (1H, s, 2-H), 8.01 (1H, s, 8-H), 7.60 (1H, d, J 9, 5-H), 6.92-7.47 (7H, m, 2'-H, 6'-H, 5 x PhH), 5.08 (2H, s, CH_2), 4.06 (6H, s, 2 x OCH_3); m/z (%) 544 (100, M+).

Example 125

6-Bromo-4-(4-benzyloxy-3,5-dibromoanilino) quinazoline

6-Bromo-4-chloroquinazoline (0.122 g; 0.5 mmol) and 3,5-dibromo-4-benzyloxyaniline (0.214 g; 0.60 mmol) were reacted in 2-propanol (5 ml) for 6 hours according to procedure C. The product was thus obtained as a cream solid (0.143 g, 51%) with mp 237-239°C; (Found C, 44.20; H, 2.66; N, 7.13. $C_{21}H_{14}Br_3N_3O.0.5H_2O$ requires C, 44.00; H, 2.62; N, 7.33); tlc (ethyl acetate:cyclohexane, 1:1) Rf 0.40; δH [$^2H_6$]-DMSO 9.95 (1H, br s, NH), 8.86 (1H, s, 5-H), 8.71 (1H, s, 2-H), 8.33 (2H, s, 2'-H, 6'-H), 8.02 (1H, d, J 9, 7-H), 7.76 (1H, d, J 9, 8-H) 7.57 (2H, s, 2 x PhH) 7.32-7.57 (3H, m, 3 x PhH), 5.05 (2H, s, CH_2); m/z (%) 563 (11, M+), 472 (30).

Example 126

4-(4-Benzyloxy-2-trifluoromethylanilino)quinazoline

4-Nitro-3-(trifluoromethyl)phenol (Aldrich) (4.14 g; 20 mmol), sodium hydride (0.544 g; 22.0 mmol) and benzyl bromide (3.6 g; 21.1 mmol) were reacted in dimethylformamide (50 ml) at 60°C for 5 hours according to Procedure E. 4-Benzyloxy-2-(trifluoromethyl)nitrobenzene was thus obtained as a pale yellow solid (5.77 g, 97%) with mp 37-39°C; (Found C, 55.74; H, 3.38; N, 4.59. $C_{14}H_{10}F_3NO_3.0.25\ H_2O$ requires C, 55.72; H, 3.48; N, 4.64); tlc (ethyl acetate) Rf 0.70.

4-Benzyloxy-2-(trifluoromethyl)nitrobenzene (1.19 g; 4.0 mmol) was reduced with hydrazine hydrate (0.600 g; 12.0 mmol) according to Procedure H. 4-Benzyloxy-2-trifluoromethylaniline (1.01 g, 95%) was obtained as a beige crystalline solid with mp 38-40°C; (Found C, 63.49; H, 4.56; N, 5.01. $C_{14}H_{12}F_3NO$ requires C, 62.92; H, 4.49; N, 5.24); tlc (ethyl acetate:cyclohexane, 1:2) Rf 0.39.

4-Chloroquinazoline (0.128 g; 0.778 mmol) and 4-benzyloxy-2-trifluoromethylaniline (0.233 g; 0.874 mmol) were reacted in 2-propanol (7 ml) for 9.5 hours according to Procedure C. The product was thus obtained as a colourless solid (0.140 g, 45%) with mp 147-148°C; (Found C, 65.94; H, 3.96; N, 10.32. $C_{22}H_{16}F_3N_3O.0.25H_2O$ requires C, 66.08; H, 4.13; N, 10.51); tlc (methanol:dichloromethane, 5:95) Rf 0.41; δH [$^2H_6$]-DMSO 11.33 (1H, br s, NH), 8.71 (1H, s, 2-H), 8.11 (1H, d, J 8, 8-H), 7.94 (1H, d, J 9, 6'-H), 7.75-7.85 (2H, m, 5-H, 7-H), 7.18-7.62 (8H, m, 6-H, 3'-H, 5'-H, 5 x PhH), 5.10 (2H, s, CH_2); m/z (%) 395 (36, M+), 326 (32), 304 (74).

Example 127

4-(4-Benzyloxy-2-trifluoromethylanilino)-6,7-dimethoxyquinazoline

4-Chloro-6,7-dimethoxyquinazoline (0.175 g; 0.78 mmol) and 4-benzyloxy-2-trifluoromethylaniline (0.233 g; 0.874 mmol) were reacted in 2-propanol (9 ml) for 14 hours according to Procedure C. The product was thus obtained as a beige solid (0.106 g, 30%) with mp 184-185°C; (Found C, 62.81; H, 4.29; N, 9.17. $C_{24}H_{20}F_3N_3O_3$ requires, C, 63.30; H, 4.40; N, 9.23); tlc (methanol:dichloromethane, 3:97) Rf 0.33; δH [$^2H_6$]-DMSO 11.21 (1H, br s, NH), 8.60 (1H, s, 2-H), 8.10 (1H, d, J 9, 6'-H), 7.09-7.48 (8H, m, 5-H, 8-H, 5'-H, 5 x PhH), 6.92 (1H, s, 3'-H), 5.11 (2H, s, CH_2), 4.07 and 4.02 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 455 (52, M+), 386 (50), 364 (100).

Example 128

4-(4-Benzyloxy-3-methylanilino)-6,7-dimethoxyquinazoline hydrochloride

A suspension of sodium hydride (0.264 g; 11 mmol) in dry dimethylformamide (10 ml) under nitrogen was treated with benzyl alcohol (1.12 g; 10.3 mmol) and the mixture stirred until evolution of hydrogen had ceased. The mixture was then treated dropwise with a solution of 2-fluoro-5-nitrotoluene (Fluorochem) (1.55 g; 10 mmol) in dry dimethyl formamide (5 ml), keeping the temperature below 10°C using external cooling. When the addition was complete, the mixture was stirred at room temperature for 18 hours and then poured into a stirred mixture of water (100 ml) and *n*-pentane (30 ml) forming a yellow solid. The solid was collected by filtration, washed and dried *in vacuo*. Crystallisation of the crude product (5% H_2O-methanol) afforded 2-benzyloxy-5-nitrotoluene as flat pale yellow needles (1.40 g, 58%) with mp 70-72°C; (Found C,

68.85; H, 5.33; N, 5.68. $C_{14}H_{13}NO_3$ requires C, 69.13; H, 5.35; N, 5.76; tlc (10% ethyl acetate/cyclohexane) Rf 0.28.

2-Benzyloxy-5-nitrotoluene (0.912 g; 3.75 mmol) was reduced with hydrazine hydrate (0.567 g; 11.25 mmol) according to Procedure H. 4-Benzyloxy-3-methylaniline (0.808 g, 99%) was obtained as a colourless oil with tlc (ethyl acetate) Rf 0.55.

4-Chloro-6,7-dimethoxyquinazoline (0.225 g; 1.0 mmol) and 4-benzyloxy-3-methylaniline (0.270 g; 1.25 mmol) were reacted in 2-propanol (6 ml) for 60 minutes according to Procedure B. The product was thus obtained as a pale yellow solid (0.418 g, 96%) with mp 253-254°C; (Found C, 65.05; H, 5.39; N, 9.43. $C_{24}H_{23}N_3O_3.HCl.0.33\ H_2O$ requires C, 64.94; H, 5.56; N, 9.47), tlc (ethyl acetate) Rf 0.20; δH [$^2H_6$]-DMSO 11.20 (1H, br s, NH), 8.76 (1H, s, 2-H), 8.30 (1H, s, 8-H), 7.28-7.53 (8H, m, 5-H, 2'-H, 6'-H, 5 x PhH), 7.10 (1H, d, J 9, 5'-H), 5.20 (2H, s, CH_2), 4.03 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3), 2.25 (3H, s, 3'-CH_3); m/z (%) 401 (33, M+), 310 (100).

Example 129

6-Bromo-4-(4-benzyloxy-3-methylanilino)quinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.244 g; 1.0 mmol) and 4-benzyloxy-3-methylaniline (0.270 g; 1.25 mmol) were reacted in 2-propanol (6 ml) for 90 minutes according to Procedure B. The product was thus obtained as a bright yellow crystalline solid (0.403 g, 88%) with mp 250-251°C; (Found C, 57.08; H, 4.15; N, 8.99. $C_{22}H_{18}BrN_3O.HCl.0.33\ H_2O$ requires C, 57.11; H, 4.28; N, 9.08); tlc (ethyl acetate) Rf 0.51; δH [$^2H_6$]-DMSO 11.50 (1H, br s, NH), 9.20 (1H, s, 5-H), 8.88 (1H, s, 2-H), 8.20 (1H, d, J 9, 7-H), 7.90 (1H, d, J 9, 8-H), 7.25-7.57 (7H, m, 2'-H, 6'-H, 5 x PhH), 7.11 (1H, d, J 9, 5'-H), 5.21 (2H, s, CH_2), 2.23 (3H, s, 3'-CH_3); m/z (%) 419, 421 (38, M+), 328, 330 (100).

Example 130

4-(4-Benzyloxy-3-fluoroanilino)quinazoline hydrochloride

2-Fluoro-4-nitrophenol (Aldrich) (3.14 g; 20 mmol), sodium hydride (0.533 g; 22 mmol) and benzylbromide (3.5 g; 21.0 mmol) were reacted in dimethylformamide (55 ml) at 65° for 1.5 hours according to Procedure E. 4-Benzyloxy-3-fluoronitrobenzene was thus obtained as a pale yellow solid (4.7 g, 95%) with mp 121-122°C; (Found C, 63.09; H, 4.14; N, 5.64. $C_{13}H_{10}FNO_3$ requires C, 63.15; H, 4.05; N, 5.67); tlc (dichloromethane) Rf 0.64.

4-Benzyloxy-3-fluoronitrobenzene (1.0 g; 4.05 mmol) was reduced with hydrazine hydrate (0.608 g; 12.15 mmol) according to Procedure H. 4-Benzyloxy-3-fluoroaniline (0.870 g, 99%) was obtained as a colourless oil; tlc (ethyl acetate) Rf 0.49.
4-Chloroquinazoline (0.151 g, 0.915 mmol) and 4-benzyloxy-3-fluoroaniline (0.220 g; 1.01 mmol) were reacted in 2-propanol (8 ml) for 4 hours according to Procedure B. The product was thus obtained as a yellow solid (0.237 g, 65%) with mp 225-226°C; (Found C, 63.25; H, 4.25; N, 10.34. $C_{21}H_{16}FN_3O.1.5HCl$ requires C, 63.04; H, 4.37; N, 10.50); tlc (ethyl acetate) Rf 0.35; δH [$^2H_6$]-DMSO 11.59 (1H, br s, NH), 8.95 (1H, s, 2-H), 8.88 (1H, d, J 9, 8-H), 7.70-8.18 (4H, m, 7-H, 5-H, 2'-H, 6'-H), 7.29-7.57 (7H, m, 6-H, 5'-H, 5 x PhH), 5.30 (2H, s, CH_2); m/z (%) 345 (56, M+), 254 (100).

Example 131

4-(4-Benzyloxy-3-fluoroanilino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.205 g; 0.913 mmol) and 4-benzyloxy-3-fluoroaniline (0.219 g; 1.01 mmol) were reacted in 2-propanol (8 ml) for 90 minutes according to Procedure B. The product was thus obtained as a cream solid (0.385 g, 94%) with mp 246-247°C; (Found C, 61.67; H, 4.70; N, 9.29. $C_{23}H_{20}FN_3O_3.HCl.0.33H_2O$ requires C, 61.67; H, 4.84; N, 9.38); tlc (ethyl acetate) Rf 0.15; δH [$^2H_6$]-DMSO 11.29 (1H, br s, PhH), 8.80 (1H, s, 2-H), 8.32 (1H, s, 8-H), 7.71 (1H, d, J 9, 6'-H), 7.30-7.52 (8H, m, 5-H, 2'-H, 5'-H, 5 x PhH), 5.29 (2H, s, CH_2), 4.05 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 405 (100, M+).

Example 132

4-(4-Benzyloxy-3-fluoroanilino)-6-bromoquinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.223 g; 0.916 mmol) and 4-benzyloxy-3-fluoroaniline (0.220 g; 1.012 mmol) were reacted in 2-propanol (8 ml) for 2.5 hours according to Procedure B. The product was thus obtained as a bright yellow solid (0.360 g, 85%) with mp 236-238°C; (Found C, 54.44; H, 3.42; N, 8.98. $C_{21}H_{15}BrFN_3O.HCl$ requires C, 54.74; H, 3.48; N, 9.12); tlc (ethyl acetate) Rf 0.49; δH [$^2H_6$]-DMSO 11.32 (1H, br s, NH), 9.12 (1H, s, 5-H), 8.90 (1H, s, 2-H), 8.20 (1H, d, J 8, 7-H), 7.90 (1H, d, J 10, 8-H), 7.32-7.58 (8H, m, 2'-H, 5'-H, 6'-H, 5 x PhH), 5.23 (2H, s, CH_2); m/z (%) 423, 425 (12, M+), 332, 334 (66).

Example 133

4-(4-Benzyloxy-3-trifluoromethylanilino)quinazoline hydrochloride

A suspension of sodium hydride (0.396 g, 16.5 mmol) in dry dimethylformamide (15 ml) under nitrogen was treated with benzyl alcohol (1.68 g; 15.45 mmol) and the

mixture stirred until evolution of hydrogen had ceased. The resulting solution was then treated dropwise with 4-fluoro-3-trifluoromethylnitrobenzene (Fluorochem) (3.44 g; 15 mmol) dissolved in dry dimethylformamide (10 ml), keeping the temperature in the range 0-5°C using external cooling. After stirring for a further 3 hours at 0°C, the mixture was stirred at room temperature for 48 hours and then poured onto crushed ice/water (150 g). The precipitated semi-solid was collected by decanting off the aqueous phase and triturated with pentane (50 ml). The resulting slurry was filtered and the product (2.26 g) dried. Crystallisation from 5% water-methanol afforded 4-benzyloxy-3-trifluoromethylnitrobenzene as almost colourless needles (2.00 g; 51%) with mp 112-113°C; (Found C, 56.41; H, 3.33; N, 4.68. $C_{14}H_{10}F_3NO_3$ requires C, 56.56; H, 3.37; N, 4.71; tlc (cyclohexane-ethyl acetate 2:1) Rf 0.44.

4-Benzyloxy-3-trifluoromethylnitrobenzene (1.39 g; 4.68 mmol) was reduced with hydrazine hydrate (0.702 g; 14.04 mmol) according to Procedure H. 4-Benzyloxy-3-trifluoro-methylaniline (1.15 g, 99%) was obtained as a pale tan oil with tlc (ethyl acetate) Rf 0.60.

4-Chloroquinazoline (0.099 g; 0.60 mmol) and 4-benzyloxy-3-trifluoromethylaniline (0.190 g; 0.78 mmol) were reacted in 2-propanol (4 ml) for 30 minutes according to Procedure B. The product was thus obtained as a pale yellow solid (0.253 g, 98%) with mp 260-262°C; (Found C, 60.60; H, 3.89; N, 9.59. $C_{22}H_{16}F_3N_3O.HCl.0.25H_2O$ requires C, 60.55; H, 4.01; N, 9.63); tlc (10% methenol/ethyl acetate) Rf 0.62; δH [$^2H_6$]-DMSO 11.43 (1H, br s, NH), 8.94 (1H, s, 2-H), 8.78 (1H, d, J 9, 8-H) 7.80-8.18 (5H, m, 5-H, 6-H, 7-H, 2'-H, 6'-H), 7.28-7.55 (6H, m, 5'-H, 5 x PhH), 5.31 (2H, s, CH_2); m/z 395 (21, M+), 304 (44).

Example 134

4-(4-Benzyloxy-3-trifluoromethylanilino)-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.135 g; 0.60 mmol) and 4-benzyloxy-3-trifluoromethylaniline (0.190 g; 0.78 mmol) were reacted in 2-propanol (4 ml) for 60 minutes according to Procedure B. The product was thus obtained as a nearly colourless solid (0.290 g, 98%) with mp 261-263°C; (Found C, 58.67; H, 4.33; N, 8.51. $C_{24}H_{20}F_3N_3O_3.HCl$ requires C, 58.59; H, 4.27; N, 8.54); tlc (10% methanol/ethyl acetate) Rf 0.53; δH [$^2H_6$]-DMSO 11.23 (1H, br s, NH), 8.81 (1H, s, 2-H), 8.47 (1H, s, 8-H), 8.06 (1H, s, 2'-H), 8.00 (1H, d, J 9, 6'-H), 7.30-7.53 (7H, m, 5-H, 5'-H, 5 x PhH), 5.34 (2H, s, CH_2), 4.09 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 455 (66, M+), 364 (100).

Example 135

4-(4-Benzyloxy-3-trifluoromethylanilino)-6-bromoquinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.146 g; 0.60 mmol) and 4-benzyloxy-3-trifluoromethyl aniline (0.190 g; 0.78 mmol) were reacted in 2-propanol (4 ml) for 30 minutes according to Procedure B. The product was thus obtained as pale lemon yellow prisms (0.295 g, 96%) with mp 243-245°C; (Found C, 52.48; H, 4.09; N, 7.37. $C_{22}H_{15}BrF_3N_3O.HCl.i$-$C_3H_7OH$ requires C, 52.58; H, 4.20; N, 7.36); tlc (10% methanol/ethyl acetate) Rf 0.69; δH [$^2H_6$]-DMSO 11.38 (1H, br s, NH), 9.12 (1H, s, 5-H), 8.90 (1H, s, 2-H), 8.21 (1H, d, J 9, 7-H), 8.10 (1H, s, 2'-H), 8.03 (1H, d, J 9, 6'-H), 7.89 (1H, d, J 9, 8-H), 7.30-7.53 (6H, m, 5'-H, 5 x PhH), 5.35 (2H, s, CH_2); m/z (%) 475, 473 (45, M+), 382 (60), 207 (55).

Example 136

4-(4-Benzyloxy-3-cyanoanilino)quinazoline hydrochloride

A suspension of sodium hydride (0.396 g; 16.5 mmol) in dry dimethylformamide (15 ml) under nitrogen was treated dropwise with benzyl alcohol (1.68 g; 15 mmol). The mixture was stirred until evolution of hydrogen had ceased and then cooled to 0°C. 2-Fluoro-5-nitrobenzonitrile (Fluorochem) (2.49 g; 15 mmol) in dry dimethylformamide (10 ml) was then added dropwise keeping the temperature at 0°C with external cooling. When the addition was complete, the mixture was stirred at 0°C for 3 hours, and at 22°C for 48 hours, and then poured onto ice/water (150 ml). The precipitated solid was collected by filtration, washed with water and dried to give an impure solid (3.97 g). Crystallisation from methanol and recrystallisation from ethyl acetate afforded 2-benzyloxy-5-nitrobenzonitrile (1.61 g, 42%) as pale yellow plates with mp 140-141°C; (Found C, 65.96; H, 3.85; N, 10.94. $C_{14}H_{10}N_2O_3$ requires C, 66.14; H, 3.94; N, 11.02); tlc (50% cyclohexane/ethyl acetate) Rf 0.50.

2-Benzyloxy-5-nitrobenzonitrile (0.254 g; 1.0 mmol) was reduced with hydrazine hydrate (0.150 g; 3.0 mmol) according to Procedure H. 4-Benzyloxy-3-cyanoaniline (0.220 g, 98%) was obtained as an off-white solid with mp 62-64°C; tlc (ethyl acetate-cyclohexane, 4:1) Rf 0.38.

4-Chloroquinazoline (0.074 g; 0.45 mmol) and 4-benzyloxy-3-cyanoaniline (0.112 g; 0.50 mmol) were reacted in 2-propanol (5 ml) for 6 hours according to Procedure B. The product was thus obtained as a yellow solid (0.121 g, 68%) with mp 222-224°C; (Found C, 66.52; H, 4.26; N, 14.35. $C_{22}H_{16}N_4O.HCl.0.5H_2O$ requires C, 66.41; H, 4.56; N, 14.09); tlc (ethyl acetate) Rf 0.36; δH [$^2H_6$]-DMSO 11.27 (1H, br s, NH), 8.92-9.11 (2H, m, 2-H, 8-H), 8.21-8.35 (2H, m, 2'-H, 6'-H), 7.98-8.19 (3H, m, 5-H, 6-H, 7-H), 7.43-7.72 (6H, m, 5'-H, 5 x PhH), 5.50 (2H, s, CH_2); m/z (%) 352 (20, M+), 261 (17).

Example 137

4-(4-Benzyloxy-3-cyanoanilino)-6,7-dimethoxyquinazoline dihydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.101 g; 0.451 mmol) and 4-benzyloxy-3-cyanoaniline (0.112 g; 0.50 mmol) were reacted in 2-propanol (6 ml) for 5 hours according to Procedure B. The product was thus obtained as a golden yellow solid (0.147 g, 67%) with mp 249-251°C; (Found C, 59.62; H, 4.48; N, 11.91. $C_{24}H_{20}N_4O_3.2HCl$ requires C, 59.38; H, 4.53; N, 11.54); tlc (ethyl acetate) Rf 0.15; δ H [$^2H_6$]-DMSO 11.22 (1H, br s, NH), 9.03 (1H, s, 2-H), 8.50 (1H, s, 8-H), 8.31 (1H, s, 5-H), 8.19 (1H, d, J 9, 6'-H), 7.49-7.74 (7H, m, 2'-H, 5'-H, 5 x PhH), 5.54 (2H, s, CH_2), 4.25-and 4.20 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 412 (27, M+), 321 (100).

Example 138

4-[4-(4-Chlorophenoxy)anilino]quinazoline hydrochloride

4-Chloroquinazoline (0.099 g; 0.60 mmol) and 4-(4-chlorophenoxy)aniline (Maybridge) (0.165g; 0.75 mmol) were reacted in 2-propanol (4 ml) for 2 hours according to Procedure B. The product was thus obtained as a pale yellow solid (0.220 g, 96%) with mp 262-265°C; (Found C, 62.70; H, 3.96; N, 10.80. $C_{20}H_{14}ClN_3O.HCl$ requires C, 62.50; H, 3.91; N, 10.94); tlc (ethyl acetate) Rf 0.45; δH [$^2H_6$]-DMSO 11.47 (1H, br s, NH), 8.90 (1H, s, 2-H), 8.84 (1H, d, J 9, 8-H), 8.10 (1H, t, J 7, 7-H), 7.97 (1H. d, J 9, 5-H), 7.86 (1H, t, J 7, 6-H), 7.77 (2H, d, J 9, 2'-H, 6'-H), 7.48 (2H, d, J 9, 3"-H, 5"-H), 7.15 (2H, d, J 8, 3'-H, 5'-H), 7.07 (2H, d, J 8, 2"-H, 6"-H); m/z (%) 347, 349 (100, M+).

Example 139

4-[4-(4-Chlorophenoxy)anilino]-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.135 g; 0.60 mmol) and 4-(4-chlorophenoxy)aniline (Maybridge) (0.165 g; 0.75 mmol) were reacted in 2-propanol (3 ml) for 2.5 hours according to Procedure B. The product was thus obtained as a yellow solid (0.256 g, 96%) with mp 258-260°C; (Found C, 59.37; H, 4.23; N, 9.52 $C_{22}H_{18}ClN_3O_3.HCl$ requires C, 59.46; H, 4.28; N, 9.46); tlc (ethyl acetate) Rf 0.22; δ H [$^2H_6$]-DMSO 11.20 (1H, br s, NH), 8.70 (1H, s, 2-H), 8.30 (1H, s, 8-H), 7.70 (2H, d, J 9, 2'-H, 6'-H), 7.42 (2H, d, J 9, 3"-H, 5"-H), 7.32 (1H, s, 5-H), 7.10 (2H, d, J 9, 3'-H, 5'-H), 7.01 (2H, d, J 9, 2"-H, 6"-H), 3.98 and 3.92 (2 x 3H, 2 x s, 2 x OCH_3) m/z (%) 407 (100, M+).

Example 140

4-[4-(2,4-Dichlorophenoxy)anilino]quinazoline hydrochloride

4-(2,4-Dichlorophenoxy)nitrobenzene (Maybridge) (1.0 g; 3.52 mmol) was reduced with hydrazine hydrate (0.529 g; 10.56 mmol) according to Procedure H. 4-(2,4-Dichlorophenoxy) aniline (0.860 g, 96%) was obtained as beige needles with mp 77-79°C; (Found C, 56.67; H, 3.42; N, 5.48. $C_{12}H_9Cl_2NO$ requires C, 56.69; H, 3.54; N, 5.51); tlc (ethyl acetate) Rf 0.52.

4-Chloroquinazoline (0.099 g; 0.60 mmol) and 4-(2,4-dichlorophenoxy)aniline (0.190 g; 0.75 mmol) were reacted in 2-propanol (5 ml) for 2.5 hours according to Procedure B. The product was thus obtained as a pale yellow solid (0.251 g, 100%) with mp 293-295°C; (Found C, 57.15; H, 3.48; N, 9.67. $C_{20}H_{13}Cl_2N_3O.HCl$ requires C, 57.35; H, 3.35; N, 10.04); tlc (ethyl acetate) Rf 0.43; δH [$^2H_6$]-DMSO 11.51 (1H, br s, NH), 8.84 (2H,-m, 2-H, 8-H), 8.06 (1H, m, 7-H), 7.94 (1H, m, 5-H), 7.67-7.86 (5H, m, 6-H, 2'-H, 6'-H, 3"-H, 5"-H), 7.35-7.49 (1H, m, 6"-H), 6.99-7.20 (2H, m, 3'-H, 5'-H); m/z (%) 380 (100, M+).

Example 141

4-[4-(2,4-Dichlorophenoxy)anilino]-6,7-dimethoxyquinazoline hydrochloride.

4-Chloro-6,7-dimethoxyquinazoline (0.135 g; 0.60 mmol) and 4-(2,4-dichlorophenoxy)aniline (0.190 g; 0.75 mmol) were reacted in 2-propanol (3 ml) for 2.5 hours according to Procedure B. The product was thus obtained as a pale yellow solid (0.286 g; 99%) with mp 250-252°C; (Found C, 54.83; H, 3.70; N, 8.72. $C_{22}H_{17}Cl_2N_3O_3.HCl$ requires C, 55.17; H, 3.76; N, 8.78); tlc (ethyl acetate) Rf 0.21; δ H [$^2H_6$]-DMSO 11.23 (1H, br s, NH), 8.85 (1H, s, 2-H), 8.30 (1H, s, 8-H), 7.83 (1H, s, 5-H), 7.75 (2H, d, J 9, 2'H, 6'-H), 7.52 (1H, d, J 9, 5"-H), 7.40 (1H, s, 3"-H), 7.11-7.33 (3H, m, 3'-H, 5'-H, 6"-H), 4.02 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3); m/z 441 (100, M+).

Example 142

6-Bromo-4-[4-(2,4-dichlorophenoxy)anilino]quinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.146 g; 0.60 mmol) and 4-(2,4-dichlorophenoxy)aniline (0.190 g; 0.75 mmol) were reacted in 2-propanol (3 ml) for 2 hours according to Procedure B. The product was thus obtained as a yellow solid (0.254 g; 85%) with mp 269-272°C; (Found C, 48.97; H, 2.58; N, 8.49. $C_{20}H_{12}BrCl_2N_3O.HCl$ requires C, 48.25; H, 2.61; N, 8.44); tlc (ethyl acetate) Rf 0.52; δH [$^2H_6$]-DMSO 10.94 (1H, br s, NH), 9.04 (1H, s, 5-H), 8.87 (1H, s, 2-H), 8.19 (1H, d, J 9, 7-H), 7.78-7.90 (4H, m, 8-H, 2'-H, 6'-H, 3"-H), 7.51 (1H, d, J 9, 5"-H), 7.10-7.25 (3H, m, 3'-H, 5'-H, 6"-H).

Example 143

4-[4-(2-Thienylmethoxy)anilino]quinazoline hydrochloride

4-Fluoronitrobenzene (28.2g, 0.20 mol), 2-thiophenemethanol (25.0g, 0.22mol) and tetrabutylammonium bromide (6.0g, 0.019 mol) were added with stirring to n-butyl ether to give a yellow solution. This was cooled to 0-5°C and stirred vigourously while 50% aqueous NaOH (100 ml, 1.25 mol) was added over 30 min (exothermic). The resulting yellow suspension was allowed to stand for 1 hour, heated on a steam bath for 1 hour and then left to stand overnight. The mixture was filtered, and the solid washed with hexane and water and dried. Recrystallisation from hot methanol gave 2-(4-nitrophenoxymethyl)-thiophene (20.1g, 43%) with mp 108-110°C ; (Found: C, 55.84; H, 3.78 N, 5.89. $C_{11}H_9NO_3S$ requires: C, 56.16; H, 3.86; N, 5.95%).

2-(4-Nitrophenoxymethyl)thiophene (0.50g, 2.13 mmol) was dissolved in 1:1 acetic acid/ethanol (60 ml), treated with Pd/C catalyst (40mg) and hydrogenated at atmospheric pressure for 2.25 hours, by which time tlc showed no remaining starting material. The catalyst was removed by filtration through Hyflo, washing with excess ethanol, and the solution concentrated in vacuo to a gum. Column chromatography on silica (40% ethyl acetate/hexane), followed by treatment with acetic acid, and trituration with petrol gave the product as a grey solid with mp 55-57°C; (Found: C, 62.44; H, 5.36 N, 6.63. $C_{11}H_{11}NOS.0.25AcOH$ requires: C, 62.70 H, 5.49; N, 6.34%); δH [$^2H_6$]-DMSO 7.35 (1H, d, J 6, 5-H), 6.96-6.98 (1H, m, 3-H), 6.85-6.90 (1H, m, 4-H), 6.59 (2H, d, J 9, 2'-H, 6'-H), 6.49 (2H, d, J 9, 3'-H, 5'-H), 4.99 (2H, s, CH_2), 3.12 (2H, v br s, NH_2); m/z (%) 206 (100 , $M+1^+$).

4-Chloroquinazoline (0.123g, 0.75 mmol) and 2-(4-aminophenoxymethyl)thiophene (0.154g, 0.75 mmol) were mixed in ethanol (15 ml) and heated to reflux for 45 minutes according to Procedure B. The yellow crystalline solid was collected by filtration, washed with cold ethanol and dried in vacuo to give the product as yellow crystals with mp 199-201°C ; (Found: C, 60.78; H, 4.56 N, 11.07. $C_{19}H_{15}N_3OS.HCl.0.4\ H_2O$ requires: C, 60.52; H, 4.46; N, 11.15%); δH [$^2H_6$]-DMSO 11.80 (1H, br s, NH), 9.00 (1H, d, J 8, 8-H), 8.89 (1H, s, 2-H), 7.99-8.13 (2H, m, 5-H, 7-H), 7.83 (1H, t, J 8, 6-H), 7.69 (2H, d, J 9, 2'-H, 6'-H), 7.58 (1H, d, J 6.5, 3"-H), 7.25 (1H, d, J 4.5, 5"-H), 7.12 (2H, d, J 9, 3'-H, 5'-H), 7.03-7.09 (1H, m, 4"-H), 5.38 (2H, s, CH_2); m/z (%) 333 (70, $M+1^+$), 236 (98), 129 (52), 97 (100); ν_{max} (KBr disc)/cm^{-1} 1612, 1564, 1508, 1373, 1240.

Example 144

6,7-Dimethoxy-4-[4-(2-thienylmethoxy)anilino]quinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.140g, 0.62 mmol) and 2-(4-aminophenoxymethyl)thiophene (prepared as described above) (0.170g, only 76% pure, 0.62 mmol) were mixed in ethanol (15 ml)
and heated to reflux for ca. 1.5 hours according to Procedure B. The yellow crystalline solid was collected by filtration, washed with cold ethanol and dried in vacuo to give the product as yellow crystals with mp 233-235oC ; (Found: C, 58.26; H, 4.63 N, 9.54. $C_{21}H_{19}N_3O_3S.HCl.0.1H_2O$ requires: C, 58.42 H, 4.72; N, 9.73%); δH [$^2H_6$]-DMSO 11.39 (1H, br s, NH), 8.78 (1H, d, J 8, 2-H), 8.39 (1H, s, 8-H), 7.85 (2H, d, J 10, 2'-H, 6'-H), 7.59 (1H, d, J 6.5, 3"-H), 7.42 (1H, s, 5-H), 7.25-7.30 (1H, m, 5"-H), 7.18 (2H, d, J 10, 3'-H, 5'-H), 7.07-7.10 (1H, m, 4"-H), 5.39 (2H, s, CH_2), 4.07 and 4.03 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 394 (100, $M+1^+$).

Example 145

4-[4-(3-Thienylmethoxy)anilino]quinazoline hydrochloride

4-Fluoronitrobenzene (28.2g, 0.20 mol), 3-thiophenemethanol (22.83g, 0.20mol) and tetrabutylammonium bromide (6.45g, 0.02 mol) were added with stirring to n-butyl ether to give a yellow solution. This was cooled to 0-5oC and stirred vigourously while 50% aqueous NaOH (100 ml, 1.25 mol) was added over 30 min (exothermic) maintaining the temperature below 5oC. The resulting rust-coloured suspension was stirred at room temperature for 1 hour, heated on a steam bath for 1 hour and then left to stand overnight. The mixture was filtered, and the red solid washed with hexane and water and dried. Recrystallisation from hot methanol gave two batches of product (totalling 18.8g, 0.080 mmol, 40%). A portion was further purified by column chromatography on silica (eluting with 20% ethyl acetate/hexane) to give 3-(4-nitrophenoxymethyl)thiophene as a pale yellow solid with mp 107-109oC; (Found: C, 56.11; H, 3.72 N, 5.93. $C_{11}H_9NO_3S$ requires: C, 56.16; H, 3.86; N, 5.95%); δH [$^2H_6$]-DMSO 8.25 (2H, d, J 10, 3'-H, 5'-H), 7.52-7.65 (2H, m, 2-H, 5-H), 7.18-7.27 (3H, m, 4-H, 2'-H, 6'-H), 5.29 (2H, s, CH_2); m/z (%) 235 (3 , M^+), 97 (100).

3-(4-Nitrophenoxymethyl)thiophene (0.50g, 2.13 mmol) was dissolved in ethanol (100 ml), treated with PtO_2 (50mg) and hydrogenated at atmospheric pressure for 16 hours. Further PtO_2 (25mg) was added and the hydrogenation continued for a further 20 hours, by which tlc showed no remaining starting material. The catalyst was removed by filtration through Hyflo, washing with excess ethanol, and the solution concentrated in vacuo. Column chromatography on silica (eluting with 50% ethyl acetate/hexane, followed by recrystallisation from ethanol/water, gave 3-

(4-aminophenoxymethyl) thiophene as a pale brown solid (0.250g, 54%) with mp 66-67°C; (Found: C, 61.29; H, 5.63 N, 6.26. $C_{11}H_{11}NOS.0.6H_2O$ requires: C, 61.14; H, 5.69; N, 6.48%); δH [$^2H_6$]-DMSO 7.50-7.58 (2H. m, 2-H, 5-H), 7.19 (1H, d, J 6, 4-H), 6.77 (2H, d, J 9, 2'-H, 6'-H), 6.58 (2H, d, J 9, 3'-H, 5'-H), 4.98 (2H, s, CH_2), 4.59 (2H, br s, NH_2); m/z (%) 205 (26 , M^+), 108 (100), 97 (92).

4-Chloroquinazoline (0.150g, 0.91 mmol) and 3-(4-aminophenoxymethyl)thiophene (0.190g, 0.93 mmol) were mixed in ethanol (15 ml) and heated to reflux for 45 minutes according to Procedure B. The yellow crystalline solid was collected by filtration, washed with cold ethanol, but appeared impure by tlc. The solid was dissolved in methanol and treated with triethylamine (solution colour changed from yellow to colourless), and the solution concentrated to give a colourless solid. Column chromatography on silica (eluted with 2:1 ethyl acetate/hexane) gave the product as the free base with mp 200-202°C; (Found: C, 67.45; H, 4.49 N, 12.13. $C_{19}H_{15}N_3OS.HCl.0.2EtOAc$ requires: C, 67.75; H, 4.77; N, 11.97%); δH [$^2H_6$]-DMSO 9.99 (1H, br s, NH), 8.69-8.77 (2H, m, 8-H, 2-H), 7.97-8.09 (2H, m, 5-H, 7-H), 7.94 (2H, d, J 9, 2'-H, 6'-H), 7.75-7.89 (3H, m, 6-H, 2"-H, 5"-H), 7.43 (1H, d, J 6, 4"-H), 7.29 (2H, d, J 9, 3'-H, 5'-H), 5.35 (2H, s, CH_2); m/z (%) 333 (46, $M+1^+$), 236 (100), 97 (62).

A portion of this material was dissolved in ethanol and treated with dilute aqueous HCl to give a yellow precipitate, which was collected by filtration, washed with water and dried to give the hydrochloride salt as a yellow solid with mp 215-217°C; (Found: C, 60.63; H, 4.23 N, 10.80. $C_{19}H_{15}N_3OS.HCl.0.5H_2O$ requires: C, 60.23; H, 4.52; N, 11.09%); δH [$^2H_6$]-DMSO 11.29 (1H, br s, NH), 8.72 (1H, s, 2-H), 8.68 (1H, d, J 9, 8-H), 7.95 (1H, t, J 9, 7-H), 7.80 (1H, d, J 9, 5-H), 7.71 (1H, t, J 9, 6-H), 7.39-7.52 (4H, m, 2'-H, 6'-H, 2"-H, 5"-H), 6.98-7.10 (3H, m, 3'-H, 5'-H, 4"-H), 5.02 (2H, s, CH_2); m/z (%) 333 (31, $M+1^+$), 236 (100), 97 (58).

Example 146

6,7-Dimethoxy-4-[4-(3-thienylmethoxy)anilino]quinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.142g, 0.63 mmol) and 3-(4-aminophenoxymethyl)thiophene (prepared as described above) (0.180g, 0.88 mmol) were mixed in ethanol (10 ml)

and heated to reflux for 30 minutes, according to Procedure B. The yellow crystalline solid was collected by filtration, washed with cold ethanol and dried in vacuo to give the product as yellow crystals with mp 247-248°C ; (Found: C, 58.68; H, 4.67 N, 9.80. $C_{21}H_{19}N_3O_3S.HCl$ requires: C, 58.68 H, 4.42; N, 9.78%); δH [$^2H_6$]-DMSO 11.36 (1H, br s, NH), 8.62 (1H, d, J 8, 2-H), 8.32 (1H, s, 8-H), 7.50-

7.65 (4H, m, 2'-H, 6'-H, 2"-H, 5"-H), 7.39 (1H, s, 5-H), 7.22 (1H, d, J 6, 4"-H), 7.10 (2H, d, J 9, 3'-H, 5'-H), 5.14 (2H, s, CH_2), 3.99 and 3.97 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 393 (29, M^+), 296 (100).

Example 147

4-[4-(Furan-2-methoxy)anilino]quinazoline hydrochloride.

4-Fluoronitrobenzene (Lancaster) (28.2 g, 200 mmol), 2-furanmethanol (Aldrich) (19.62 g, 200 mmol) and tetrabutylammonium bromide (Aldrich) (6.45 g, 20 mmol) were added in turn to n-butyl ether (250 ml) and cooled to 0-5°C before the slow addition of 50% aqueous sodium hydroxide (100 ml) with vigorous stirring. After complete addition of base the reaction mixture was stirred at room temperature for 60 mins by which time a very dense precipitate had formed. The reaction mixture was heated on a steam bath for 60 mins then allowed to cool overnight. The crude 2-(4-nitrophenoxymethyl)furan was collected by filtration and recrystallised from ethanol (150 mls) to give cream coloured needles, mp 96-97°C; Found: C, 59.95; H, 4.12; N, 6.35. $C_{11}H_9NO_4.0.1EtOH$ requires: C, 60.11; H, 4.32;N, 6.26.); δH [$^2H_6$]-DMSO 8.19 (2H, d, J 10, 3'-H, 5'-H), 7.72 (1H, s, 5-H), 7.25 (2H, d, J 10, 2'-H, 6'-H), 6.68 (1H, t, J 2, 4-H), 6.49 (1H, d, J 2, 3-H), 5.25 (2H, s, CH_2); m/z (%) 219 (1, M^+), 81 (100).

2-(4-Nitrophenoxymethyl)furan (0.50 g, 2.30 mmo) was dissolved in ethyl acetate (60 ml) treated with Pd/C 10% (0.040 g) and hydrogenated at atmospheric pressure until the total amount of H_2 taken up was 140 mls. Tlc showed no remaining starting material. The catalyst was removed by filtration through Hyflo, washing with excess ethyl acetate, and the solution was concentrated in vacuo to give 2-(4-aminophenoxymethyl)furan. as a brownish solid. No further attemp was made to purify the product and it was used immediately; m/z (%) 189 (53, M^+), 108 (93), 81 (100).

4-Chloroquinazoline (0.160 g, 0.97 mmol) and 2-(4-aminophenoxymethyl)furan (0.183 g, 0.97 mmol) were reacted in ethanol (10 ml) for 40 minutes according to Procedure B. The product was obtained as a bright yellow solid, mp 185-187°C; (Found: C, 61.14; H, 4.78; N, 11.30. $C_{19}H_{15}N_3O_2.HCl.H_2O$ requires: C, 61.37 H, 4.88 N, 11.30.); δH [$^2H_6$]-DMSO 11.60 (1H, br s, NH), 8.80-8.95 (2H, m, 2-H, 8-H), 8.09 (1H, t, J 8, 7-H), 7.96 (1H, d, J 9, 5-H), 7.86 (1H, t, J 8, 6-H), 7.69 (1H, s, 5"-H), 7.65 (2H, d, J 10, 2'-H, 6'-H), 7.13 (2H, d, J 10, 3'-H, 5'-H), 6.61 (1H, d, J 2, 3"-H), 6.47 (1H, t, J 2, 4"-H), 5.11 (2H, s, CH_2); m/z (%) 317 (28, M^+), 236 (100), 81 (74).

Example 148

6,7-Dimethoxy-4-[4-(furan-2-methoxy)anilino]quinazoline hydrochloride.

4-Chloro-6,7-dimethoxyquinazoline (0.218 g, 0.97 mmol) and 2-(4-aminophenoxymethyl)furan (prepared as described above) (0.183 g, 0.97 mmol) were reacted in ethanol (10 ml) for 30 minutes according to Procedure B. The product was obtained as bright yellow crystals with mp 237-238°C; (Found: C, 60.75; H, 4.80; N, 10.06. $C_{21}H_{19}N_3O_4.HCl$ requires C, 60.95; H, 4.84; N, 10.16); δH [$^2H_6$]-DMSO 11.29 (1H, br s, NH), 8.73 (1H, s, 2-H), 8.31 (1H, s, 8-H), 7.69 (1H, s, 5"-H), 7.51 (2H, d, J10, 2'-H, 6'-H), 7.39 (1H, s, 5-H), 7.13 (2H, d, J10, 3'-H, 5'-H), 6.51 (1H, d, J 2, 3-H), 6.49 (1H, t, J 2, 4-H), 5.09 (2H, s, CH_2), 4.01 and 3.99 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 377 (11, M^+), 296 (100), 81 (24).

Example 149

4-[4-(Furan-3-methoxy)anilino]quinazoline hydrochloride

4-Fluoronitrobenzene (Lancaster) (28.2 g, 200 mmol), 3-furanmethanol (Aldrich) (19.62 g, 200 mmol) and tetrabutylammonium bromide (6.45 g, 20 mmol) were added in turn to n-butyl ether (250 ml). The solution was cooled to 0-5°C and 50% aqueous sodium hydroxide (100 ml) was added slowly with vigorous stirring. After complete addition of base and stirring at room temperature for 60 mins the reaction mixture was heated on a steam bath for 60 mins then allowed to stand at 4°C overnight. The 3-(nitrophenoxymethyl)furan was collected by filtration, recrystallised from ethanol, and dried in vacuo to give cream coloured needles. mp 82-83°C; (Found: C, 59.80; H, 4.10; N, 6.28. $C_{11}H_9NO_4.0.1H_2O$ requires: C, 59.78; H, 4.20; N, 6.34.); δH [$^2H_6$]-DMSO 8.20 (2H, d, J 10, 3'-H, 5'-H), 7.82 (1H, s, 5-H), 7.68 (1H, s, 2-H), 7.22 (2H, d, J 10, 2'-H, 6'-H), 6.59 (1H, s, 4-H), 5.15 (2H, s, CH_2); m/z (%) 219 (20, M^+), 81 (100).

3-(Nitrophenoxymethyl)furan (1.00 g, 4.6 mmol) was dissolved in ethyl acetate (100 ml), treated with Pd/C 10% (0.080g) and hydrogenated at atmospheric pressure for 45 minutes. Tlc showed complete comsumpion of starting material, the catalyst was removed by filtration through Hyflo, washing with excess ethyl acetate. Evaporation of the solvent in vacuo gave a gum. Addition of 70% aqueous acetic acid (10 ml) followed by evaporation in vacuo gave 3-(aminophenoxymethyl)furan as a greyish solid. mp 54-56°C; (Found:C, 64.84; H, 6.01; N, 6.71. $C_{11}H_{11}NO_2.0.8H_2O$ requires: C, 64.90; H, 6.19; N, 6.88.); δH [$^2H_6$]-DMSO 7.67 and 7.60 (2 x 1H, 2 x s, 2-H, 5-H), 6.69 (2H, d, J 10, 2'-H, 6'-H), 6.40-6.57 (3H, m 4-H, 3'-H, 5'-H), 4.28 (2H, s, CH_2); m/z (%) 189 (23, M^+), 108 (100), 81 (98), 53 (96).

4-Chloroquinazoline (0.160 g, 0.97 mmol) and 3-(aminophenoxymethyl)furan (0.183 g, 0.97 mmol) were reacted in ethanol (10 ml) for 45 minutes according to Procedure B. The product was obtained as a bright yellow crystalline solid, mp 216-217°C; (Found: C, 63.74; H, 4.47; N, 11.72. $C_{19}H_{15}N_3O_2.HCl.0.2H_2O$

requires: C, 63.85; H, 4.62; N, 11.76.); 11.54 (1H, br s, NH), 8.92 (1H, d, J 9, 8-H), 8.88 (1H, s, 2-H), 8.09 (1H, t, J 8, 7-H), 7.99 (1H, d, J 8, 5-H), 7.78-7.90 (2H, m, 6-H, 5"-H), 7.60-7.69 (3H, m, 2'-H, 6'-H, 2"-H), 7.12 (2H, d, J 10, 3'-H, 5'-H), 6.58 (1H, s, 4"-H), 5.12 (2H, s, CH_2); m/z (%) 317 (84, M^+), 236 (100).

Example 150

6,7-Dimethoxy-4-[4-(furan-3-methoxy)anilino]quinozoline Hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.218 g' 0.97 mmol) and 3-(4-aminophenoxymethyl)furan (0.183 g, 0.97 mmol) were reacted in ethanol (10 ml) for 45 minutes according to Procedure B. The product was obtained as yellow crystals, mp 233-235°; (Found: C, 60.07; H, 4.86; N, 10.18. $C_{21}H_{19}N_3O_4.HCl.0.25H_2O$ requires: C, 60.29; H, 4.94; N, 10.04.); 11.25 (1H, br s, NH), 8.70 (1H, s, 2-H), 8.32 (1H, s, 8-H), 7.80 (1H, s, 5"-H), 7.68 (1H, s, 2"-H), 7.59 (2H, d, J 9, 2'-H, 6'-H), 7.38 (1H, s, 5-H), 7.09 (2H, d, J 9, 3'-H, 5'-H), 6.59 (1H, s, 4-H), 5.01 (2H, s, CH_2), 4.01 and 3.99 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 377 (56, M^+), 296 (100).

Example 151

(S)-4-{4-[(2-Oxo-4-oxazolinyl)methyl]anilino}quinazoline hydrochloride

4-Chloroquinazoline (0.164g, 1.00 mmol) and (S)-4-(4 aminobenzyl)-1,3-oxazolidin-2-one (prepared as reported in PCT International Patent WO 91 18,897) (0.166g, 1.0 mmol) were reacted in ethanol (20 ml) for 1.5 hours according to Procedure B. The pale yellow solid thus obtained was the product (0.231g, 65%). A portion was recrystallised from ethanol to give a yellow crystalline solid with mp 217°C (decomp.); (Found: C, 60.59; H, 4.84 N, 15.54. $C_{18}H_{16}N_4O_2.HCl$ requires: C, 60.59; H, 4.80; N, 15.71%); δH [$^2H_6$]-DMSO 11.77 (1H, br s, NH), 9.01 (1H, d, J 9, 8-H), 8.90 (1H, s, 2-H), 8.10 (1H, t, J 8, 7-H), 8.01 (1H, d, J 8, 5-H), 7.86 (1H, t, J 8, 6-H), 7.79 (1H, s, CONH), 7.69 (2H, d, J 9, 2'-H, 6'-H), 7.38 (2H, d, J 9, 3'-H, 5'-H), 4.34 (1H, t, J 8, 4"-CH), 4.08-4.17 (1H, m, 5"-H), 4.05 (1H, dd, J 9, 7.5, 5"-H), 2.75-2.93 (2H, m, $C_6H_4CH_2$); m/z (%) 320 (18, M^+), 234 (100), 106 (48); νmax (KBr disc)/cm^{-1} 1758, 1634, 1616, 1564, 1439, 1377.

Example 152

(S)-6,7-Dimethoxy-4-{4-[(2-oxo-4-oxazolinyl)methyl]anilino}quinazoline hydrochloride

4-Chloro-6,7-dimethyoxyquinazoline (0.224g, 1mmol) and (S)-4-(4 aminobenzyl)-1,3-oxazolidin-2-one (prepared as reported in PCT International Patent WO 91 18,897)

(0.179g, 1mmol) were reacted in ethanol (10ml) and for 45 minutes according to Procedure B. The product was obtained as a pale yellow solid, which decomposed at 211°C. (Found: C, 55.43; H, 5.05; N, 12.78. $C_{20}H_{20}N_4O_4.HCl.0.8H_2O$ requires: C, 55.70; H, 5.28; N, 12.99); δH [$^2H_6$]-DMSO 11.37 (1H, br s, NH), 8.89 (1H. s, 2-H), 8.44 (1H, s, 8-H), 7.89 (1H, s, CONH), 7.75 (2H, d, J 9, 2'-H, 6'-H), 7.40-7.50 (3H, m, 5-H, 3'-H, 5'-H), 4.41 (1H, t, J 9, 4"-CH), 4.05-4.28 (8H, m, 2 x OCH_3, 5"-H_2), 2.89-3.02 (2H. m, $C_6H_4CH_2$); m/z (%) 380 (18, M^+), 294 (100), 106 (34).

Example 153

(R/S)-4-{4-[(3-Methyl-2-oxo-4-oxazolidinyl)methyl]anilino}quinazoline hydrochloride

4-Chloroquinazoline (0.165g, 1mmol) and 3-methyl-4-(4-aminobenzyl)-2-oxazolidinone (prepared as reported in PCT International Patent WO 91 18,897) (0.206g, 1mmol) were reacted in ethanol (10ml) for 45 minutes according to Procedure B. The product was obtained as a bright yellow solid, mp 236-238°C. (Found: C, 61.30; H, 5.10; N, 14.88. $C_{19}H_{18}N_4O_2.HCl$ requires C, 61.55; H, 5.13; N, 15.11); δH [$^2H_6$]-DMSO 11.75 (1H, br s, NH), 8.97 (1H, d, J 9, 8-H), 8.92 (1H, s, 2-H), 8.10 (1H, t, J 8, 7-H), 8.01 (1H, d, J 9, 5-H), 7.85 (1H, t, J 8, 6-H), 7.69 (2H, d, J 9, 2'-H, 6'-H), 7.39 (2H, d, J 9, 3'-H, 5'-H), 4.25 (1H, t, J 8, 4"-CH), 3.93-4.10 (2H, m, 5"-H_2), 3.09 (1H, dd, J 12.5, 6, one of $C_6H_4CH_2$), 2.78-2.88 (4H, m, NCH_3, one of $C_6H_4CH_2$); m/z (%) 334 (34, M^+), 234 (100).

Example 154

(R/S)-6,7-Dimethoxy-4-{4-[(3-methyl-2-oxo-4-oxazolidinyl)methyl]anilino}quinazoline hydrochloride

6,7-Dimethoxy-4-chloroquinazoline (0.112g, 0.5mmole) and 3-methyl-4-(4-aminobenzyl)-2-oxazolidinone (prepared as reported in PCT International Patent WO 91 18,897) (0.103g, 0.5 mmol) were reacted in ethanol (10ml) for 45 minutes according to Procedure B. The product was obtained as a pale cream solid, mp 243-245°C. (Found: C, 58.71; H, 5.34; N, 12.95. $C_{21}H_{22}N_4O_4.HCl$ requires: C, 58.54; H, 5.34; N, 13.01); δH [$^2H_6$]-DMSO 11.29 (1H, s, NH), 8.79 (1H, s, 2-H), 8.30 (1H, s, 8-H), 7.67 (2H, d, J 9, 2'-H, 6'-H), 7.31-7.40 (3H, m, 5-H, 3'-H, 5'-H), 4.24 (1H, t, J 8, 4"-CH), 3.96-4.12 (8H, m, 2 x OCH_3, 5"-H_2), 3.09 (1H, dd, J 12.5, 6, one of $C_6H_4CH_2$), 2.78-2.89 (4H, m, NCH_3, one of $C_6H_4CH_2$); m/z (%) 334 (59, M^+), 294 (100), 106 (84).

Example 155

4-[4-(2-Thiazolyl)aminosulphonyl]anilinoquinazoline hydrochloride

4-Chloroquinazoline (0.164g; 1mmole) and N^1-(2-thiazolyl)sulfanilamide (Aldrich) (0.255g, 1mmol) were mixed in ethanol (10ml) and heated to reflux for 40 minutes according to Procedure B. The product was obtained as a a bright yellow solid, mp 261-263°C. (Found: C, 48.48; H, 3.36; N, 16.42. $C_{17}H_{13}N_5O_2S_2$.HCl requires: C, 48.60; H, 3.34; N, 16.68); δH [$^2H_6$]-DMSO 12.75 (1H, br s, SO_2NH), 11.63 (1H, br s, NH), 8.88-8.98 (2H, m, 2-H, 8-H), 8.10 (1H, t, J 8, 7-H), 7.82-8.04 (6H, m, 5-H, 6-H, 2'-H, 3'-H, 5'-H, 6'-H), 7.24 and 6.85 (2 x 1H, 2 x d, J 5.5, 4"-H, 5"-H); m/z (%) 383 (23, M^+), 319 (68), 220 (90), 92 (68), 44 (100).

Example 156

6,7-Dimethoxy-4-[4-(2-thiazolyl)aminosulphonyl]anilinoquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.224g; 1mmol) and N^1-(2-thiazolyl)sulfanilamide (Aldrich) (0.255g; 1mmol) were reacted in ethanol (10ml) for 40 minutes according to Procedure B. The product was obtained as a pale yellow solid, mp 263-265°C. (Found: C, 47.26; H, 3.73; N, 14.40. $C_{17}H_{17}N_5O_4S_2$.HCl requires: C, 47.52; H, 3.75; N, 14.59) δH [$^2H_6$]-DMSO 12.72 (1H, v br s, SO_2NH), 11.40 (1H, br s, NH), 8.82 (1H, s, 2-H), 8.35 (1H, s, 8-H), 7.83-7.98 (4H, m, 2'-H, 3'-H, 5'-H, 6'-H), 7.39 (1H, s, 5-H), 7.24 and 6.84 (2 x 1H, 2 x d, J 5.5, 4"-H, 5"-H), 4.03 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 443 (24, M^+), 379 (50), 280 (100).

Example 157

4-[4-(1,2,3-Thiadiazol-4-yl)anilino]quinazoline hydrochloride

4-Chloroquinazoline (0.164g, 1mmol) and 4-(4-aminophenyl)-1,2,3-thiadiazole (Maybridge) (0.177g, 1mmol) were reacted in ethanol (10ml) for 45 minutes according to Procedure B. The product was obtained as a bright yellow solid, which decomposed at 242°C; (Found: C, 56.27; H, 3.57; N, 20.40. $C_{16}H_{11}N_5S$.HCl requires: C, 56.23; H, 3.51; N, 20.50); δH [$^2H_6$]-DMSO 11.65 (1H, br s, NH), 9.65 (1H, s, 5"-H), 8.90-8.99 (2H, m, 2-H, 8-H), 8.25 (2H, d, J 10, 3'-H, 5'-H), 8.09 (1H, t, J 8, 7-H), 7.93-8.02 (3H, m, 5-H, 2'-H, 6'-H), 7.88 (1H, t, J 8, 6-H); m/z (%) 305 (24, M^+), 276 (100).

Example 158

6,7-Dimethoxy-4-[4-(1,2,3-thiadiazol-4-yl)anilino]quinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.244g; 1mmol) and 4-(4-aminophenyl)-1,2,3-thiadiazole (Maybridge) (0.177g; 1mmol) were reacted in ethanol (10ml) for 40 minutes according to Procedure B. The product was obtained as a pale yellow solid, which decomposed at 350°C. (Found: C, 53.73; H, 3.99; N, 17.31. $C_{16}H_{11}N_5O_2S$.HCl requires: C, 53.77; H, 3.98; N, 17.43); δH [$^2H_6$]-DMSO 11.43 (1H, br s, NH), 9.60 (1H,

s, 5"-H), 8.82 (1H, s, 2-H), 8.39 (1H, s, 8-H), 8.22 (2H, d, J 9, 3'-H, 5'-H), 7.95 (2H, d, J 9, 2'-H, 6'-H), 7.38 (1H, s, 5-H), 4.02 and 3.99 (2 x 3H, , 2 x s, 2 x OCH_3); m/z (%) 365 (21, M^+), 336 (100).

Example 159

4-(4-Cyclohexyl)anilinoquinazoline hydrochloride

4-Chloroquinazoline (0.164g, 1mmol) and 4-cyclohexylaniline (Aldrich) (0.175g, 1mmol) were reacted in ethanol (10ml)for 45 minutes according to Procedure B. The product was obtained as a white solid, mp 273-275°C. (Found: C. 70.51; H, 6.64; N, 12.17. $C_{20}H_{21}N_3$.HCl requires: C; 70.70; H, 6.48; N, 12.37); δH [$^2H_6$]-DMSO 11.55 (1H, br s, NH), 8.87-8.92 (2H, m, 2-H, 8-H), 8.13 (1H, t, J 8, 7-H), 7.98 (1H, d, J 9, 5-H), 7.86 (1H, t, J 8, 6-H), 7.63, (2H, d, J 9, 2'-H, 6'-H), 7.34 (2H. d, J 9, 3'-H, 5'-H), 2.49-2.61 (1H, m, 1"-H), 1.63-1.90 (5H, m) and 1.19-1.52 (5H, m) (cyclohexyl CH_2 groups); m/z (%) 302 (100).

Example 160

4-(4-Cyclohexyl)anilino-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxy quinazoline (0.224g, 1mmol) and 4-cyclohexylaniline (Aldrich) (0.175g, 1mmol) were reacted in ethanol (10ml) for 45 minutes according to Procedure B. The product was obtained as a cream coloured solid, mp 264-265°C, (Found: C; 65.76; H, 6.57; N, 10.43. $C_{22}H_{25}N_3O_2$.HCl. 0.01 EtOH requires: C, 66.06; H, 6.56; N, 10.49); δH [$^2H_6$]-DMSO 10.89 (1H, br s, NH), 8.72 (1H, s, 2-H), 8.12 (1H, s, 8-H), 7.58, (2H, d, J 9, 2'-H, 6'-H), 7.32 (2H, d, J 9, 3'-H, 5'-H), 7.29 (1H, s, 5H) 3.99 (6H, s, 2 x OCH_3), 2.50-2.60 (1H, m, 1"-H), 1.68-1.88 (5H, m) and 1.10-1.55 (5H, m) (cyclohexyl CH_2 groups); m/z (%) 362 (100).

Example 161

4-[4-(Cyclohexylmethoxy)anilino]quinazoline hydrochloride

4-Nitrophenol (4.17g, 30 mmol) was added portionwise to a suspension of sodium hydride (0.80g, 33 mmol) in dry DMF under a nitrogen atmosphere. When hydrogen evolution had ceased, the clear yellow solution was treated with cyclohexylmethyl bromide (5.31g, 31 mmol) and the mixture was stirred at 65-70°C for 28 hours. The reaction mixture was poured onto ice-water (200g) with stirring, and a pale yellow solid precipitated. This was collected by filtration, washed with water and pentane, and dried to give 4-(cyclohexylmethoxy)nitrobenzene (4.16g, 59%) with mp 77-78°C ; (Found: C, 65.94; H, 7.383; N, 5.95. $C_{13}H_{17}NO_3$ requires: C, 66.38; H, 7.23; N, 5.96%).

4-(Cyclohexylmethoxy)nitrobenzene (0.879g, 3.74 mmol) was added portionwise and alternately with hydrazine hydrate (0.567g, 11.25mmol) to a suspension of Raney nickel (ca.0.50g), pre-washed with methanol (3 x 10ml), in methanol (15ml), maintaining the temperature of the reaction below 35°C. Stirring was continued until nitrogen evolution had ceased (10 min), and then at 40°C for 10 min to destroy any excess hydrazine hydrate. The catalyst was removed by filtration through Hyflo, washing with excess methanol, and the solution concentrated in vacuo, to give 4-(cyclohexylmethoxy)aniline, which was clean by tlc, and was not purified or characterised further.

4-Chloroquinazoline (0.165g, 1.00 mmol) and 4-(cyclohexylmethoxy)aniline (one third of the material prepared, ca. 1.25 mmol) were mixed in 2-propanol (5 ml) and heated to reflux for 3.5 hours according to Procedure B. The precipitate was collected by filtration, washed with cold 2-propanol/ethanol (1:1) and ether, and dried in vacuo to give the product as a yellow solid (0.322g, 87%) with mp 255-257°C ; (Found: C, 68.02; H, 6.59 N, 11.19. $C_{21}H_{23}N_3O.HCl$ requires: C, 68.20; H, 6.49; N, 11.36%); δH [$^2H_6$]-DMSO 11.64 (1H, br s, NH), 8.93 (1H, d, J 9, 8-H), 8.85 (1H, s, 2-H), 8.07 (1H, t, J 8, 7-H), 7.98 (1H, d, J 8, 5-H), 7.82 (1H, t, J 8, 6-H), 7.62 (2H, d, J 9, 2'-H, 6'-H), 7.04 (2H, d, J 9, 3'-H, 5'-H), 3.82 (2H, d, J 7, CH_2), 1.58-1.89 (6H, m) and 0.94-1.35 (5H, m) (cyclohexyl).

Example 162

4-[4-(Cyclohexylmethoxy)anilino]-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.225g, 1.00 mmol) and 4-(cyclohexylmethoxy)aniline (prepared as described above) (one third of the material prepared, ca. 1.25 mmol) were mixed in 2-propanol (5 ml) and heated to reflux for ca. 4.5 hours according to Procedure B. The precipitate was collected by filtration, washed with cold 2-propanol/ethanol (1:1) and ether, and dried in vacuo to give the product as a pale cream solid (0.388g, 88%) with mp 246-247°C ; (Found: C, 62.98; H, 6.54 N, 9.58. $C_{23}H_{27}N_3O_3.HCl.0.5H_2O$ requires: C, 62.94 H, 6.61; N, 9.57%); δH [$^2H_6$]-DMSO 10.98 (1H, br s, NH), 8.71 (1H, d, J 8, 2-H), 8.21 (1H, s, 8-H), 7.58 (2H, d, J 9, 2'-H, 6'-H), 7.32 (1H, s, 5-H), 7.03 (2H, d, J 9, 3'-H, 5'-H), 3.99 and 3.98 (2 x 3H, 2 x s, 2 x OCH_3), 3.85 (2H, d, J 7, CH_2), 1.61-1.92 (6H, m) and 0.99-1.39 (5H, m) (cyclohexyl); m/z (%) 393 (78, M^+), 296 (100).

Example 163

4-[3-(2-Methyl-4-pyrimidinyl)anilino]quinazoline hydrochloride

4-Chloroquinazoline (0.165 g; 1.0 mmol) and 4-(3-aminophenyl)-2-methylpyrimidine (Maybridge Chemicals) (0.185 g; 1.0 mmol) were reacted in 2-propanol (5 ml) for 45 minutes according to Procedure B. The product was thus obtained as a cream powder (0.343 g; 98%) with mp 257-259°C (dec.); (Found C, 64.45; H, 4.62; N, 19.68. $C_{19}H_{15}N_5.HCl.0.25H_2O$ requires C, 64.40; H, 4.66; N, 19.77); tlc (10% methanol/ethyl acetate) Rf 0.34; δH [$^2H_6$]-DMSO 11.34 (1H, br s, NH), 9.02 (1H, d, J 9, 8-H), 8.96 (1H, s, 2-H), 8.80 (1H, d, J 7, 6"-H), 8.52 (1H, s, 2'-H), 7.60-8.18 (7H, m, 5-H, 6-H, 7-H, 4'-H, 5'-H, 6'-H, 5"-H), 2.70 (3H, s, 2'-CH_3); m/z (%) 313 (56, M+), 312 (100, M-1).

Example 164

4-[4-(1,3-Dioxolan-2-yl)methoxy]quinazoline hydrochloride

A suspension of sodium hydride (1.06 g; 44 mmol) in dry dimethylformamide (100 ml) under nitrogen was treated portionwise with 4-nitrophenol (4.92 g; 35 mmol) and the mixture stirred until evolution of hydrogen had ceased. 2-Bromomethyl-1,3-dioxolane (6.68 g; 40 mmol) and potassium iodide (3 g) were then added and the mixture stirred at 95°C for 28 hours. After cooling to 30°C, the reaction mixture was poured onto stirred crushed ice/water (300 g) when a pale cream solid was precipitated. The solid was collected by filtration, washed with water until the filtrates were neutral and the solid dried *in vacuo* to give 4-(1,3-dioxolan-2-yl)methoxynitrobenzene (4.61 g, 59%) with mp 117-118°C; (Found C, 53.30; H, 4.91; N, 6.21. $C_{10}H_{11}NO_5$ requires C, 53.33; H, 4.89; N, 6.22); tlc (ethyl acetate) Rf 0.58.

4-(1,3-Dioxolan-2-yl)methoxynitrobenzene (1.13 g; 5.0 mmol) was reduced with hydrazine hydrate (0.756 g; 15.0 mmol) according to Procedure H. 4-(1,3-Dioxolan-2-yl)methoxy aniline (0.975 g, 100%) was obtained as a colourless oil, tlc (ethyl acetate) Rf 0.42.

4-Chloroquinazoline (0.165 g; 1.0 mmol) and 4-(1,3-dioxolan-2-yl)methoxyaniline (0.243 g; 1.25 mmol) were reacted in 2-propanol (5 ml) for 60 minutes according to Procedure B. The product was thus obtained as yellow needles (0.319 g, 89%) with mp 241-243°C (effervesc.); (Found C, 59.97; H, 5.14; N, 11.52. $C_{18}H_{17}N_3O_3.HCl$ requires C, 60.08; H, 5.00; N, 11.68); tlc (ethyl acetate) Rf 0.27; δH [$^2H_6$]-DMSO 11.57 (1H, br s, NH), 8.78 (1H, d, J 7, 8-H), 8.70 (1H, s, 2-H), 7.64-8.02 (3H, m, 5-H, 6-H, 7-H), 7.51 (2H, d, J 9, 2'-H, 6'-H), 6.89 (2H, d, J 9, 3'-H, 5'-H), 5.10 (1H, m, 2"-H), 4.93 (2H, m, 4'-OCH_2), 3.66-3.88 (4H, m, 2 x OCH_2); m/z (%) 323 (100, M+), 250 (92).

Example 165

4-[4-(1,3-Dioxolan-2-yl)methoxy]-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.225 g; 1.0 mmol) and 4-(1,3-dioxolan-2-yl)methoxyaniline (0.243 g; 1.25 mmol) were reacted in 2-propanol (5 ml) for 75 minutes according to Procedure B. The product was thus obtained as a cream solid (0.407 g, 97%) with mp 248-249°C (effervesc.); (Found C, 57.14; H, 5.29; N, 9.99. $C_{20}H_{21}N_3O_5.HCl$ requires C, 57.21; H, 5.24; N, 10.01); tlc (ethyl acetate) Rf 0.13; δH [$^2H_6$]-DMSO 11.40 (1H, br s, NH), 8.75 (1H, s, 2-H), 8.39 (1H, s, 8-H), 7.62 (2H, d, J 9, 2'-H, 6'-H), 7.40 (1H, s, 5-H), 7.08 (2H, d, J 9, 3'-H, 5'-H), 5.21-5.28 (1H, m, 2"-H), 3.84-4.12 (12H, m, 3 x CH_2, 2 x OCH_3); m/z (%) 383 (100, M+), 310 (92).

Example 166

6-Bromo-4-[4-(1,3-dioxolan-2-yl)methoxy]quinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.244 g; 1.0 mmol) and 4-(1,3-dioxolan-2-yl)methoxyaniline (0.243 g; 1.25 mmol) were reacted in 2-propanol (5 ml) for 60 minutes according to Procedure B. The product was thus obtained as bright yellow needles (0.383 g, 87%) with mp 252-254°C; (Found C, 49.05; H, 3.81; N, 9.43. $C_{18}H_{16}BrN_3O_3.HCl$ requires C, 49.25; H, 3.87; N, 9.57); tlc (ethyl acetate) Rf 0.38; δ H [$^2H_6$]-DMSO 11.44 (1H, br s, NH), 9.20 (1H, s, 5-H), 8.89 (1H, s, 2-H), 8.24 (1H, m, 7-H), 7.94 (1H, m, 8-H), 7.16 (2H, d, J 9, 2'-H, 6'-H), 7.08 (2H, d, J 9, 3'-H, 5'-H), 5.21 (1H, m, 2"-H), 3.81-4.10 (6H, m, 3 x CH_2); m/z (%) 401, 403 (62, M+), 330, 328 (48).

Example 167

4-[4-(1-Morpholinyl)anilino]quinazoline hydrochloride

4-Chloroquinazoline (0.165 g; 1.0 mmol) and *N*-(4-aminophenyl)morpholine (Maybridge Chemicals) (0.178 g; 1.0 mmol) were reacted in 2-propanol for 60 minutes according to Procedure B. The product was thus obtained as a yellow solid (0.340 g, 98%) with mp 229-230°C (dec.); (Found C, 59.87; H, 5.81; N, 15.25. $C_{18}H_{18}N_4O.HCl.H_2O$ requires C, 59.91; H, 5.82; N, 15.53); tlc (10% methanol/ethyl acetate) Rf 0.39; δH [$^2H_6$]-DMSO 11.58 (1H, br s, NH), 8.90 (1H, d, J 9, 8-H), 8.85 (1H, s, 2-H), 8.05-8.14 (1H, m, 7-H), 7.99 (1H, d, J 9, 5-H), 7.86 (1H, t, J 7, 6-H), 7.60 (2H, d, J 9, 2'-H, 6'-H), 7.06 (2H, d, J 9, 3'-H, 5'-H), 3.72-3.82 (4H, m, 2 x CH_2), 3.13-3.20 (4H, m, 2 x CH_2); m/z (%) 306 (100, M+), 247 (98), 219 (26).

Example 168

4-[4-(1-Piperidinyl)anilino]quinazoline hydrochloride

4-Chloroquinazoline (0.165 g; 1.0 mmol) and *N*-(4-aminophenyl)piperidine (Maybridge Chemicals) (0.176 g; 1.0 mmol) were reacted in 2-propanol (5 ml) for 75 minutes according to Procedure B. The product was thus obtained as a yellow solid (0.218 g, 64%) with mp 228-230°C (dec.); (Found C, 66.21; H, 6.07; N, 16.21. $C_{19}H_{20}N_4.HCl.0.25H_2O$ requires C, 66.09; H, 6.23; N, 16.23); tlc (10% methanol/ethyl acetate) Rf 0.46; δH [$^2H_6$]-DMSO 11.30 (1H, br s, NH), 8.83 (1H, d, J 9, 8-H), 8.80 (1H, s, 2-H), 7.55-8.10 (5H, m, 5-H, 6-H, 7-H, 2'-H, 6'-H), 7.09-7.22 (2H, m, 3'-H, 5'-H), 3.20-3.31 (4H, m, 2"-H_2, 6"-H_2), 1.56-1.76 (6H, m, 3"-H_2, 4"-H_2, 5"-H_2); m/z (%) 304 (98, M+) 303 (100, M-1$^+$), 247 (76).

Example 169

4-[4-(1,3-Dioxan-2-ylethoxy)anilino]quinazoline hydrochloride

A suspension of sodium hydride (1.06 g; 44 mmol) in dry dimethylformamide (100 ml) under nitrogen was treated portionwise with 4-nitrophenol (4.92 g; 35 mmol) and the mixture stirred until evolution of hydrogen had ceased. 2-(2-Bromoethyl)-1,3-dioxane (7.8 g; 40 mmol) and potassium iodide (2 g) were added and the mixture stirred at 85°C for 16 hours, cooled to 25°C and poured into stirred ice/water (200 g) when a pale cream solid was precipitated. The solid was collected by filtration, washed with cold water and dried to give 4-[2-(1,3-dioxan-2-yl)ethoxy]nitrobenzene as a pale cream powder (7.22 g; 82%) with mp 89-90°C; (Found C, 57.00; H, 6.07; N, 5.56. $C_{12}H_{15}NO_5$ requires C, 56.91; H, 5.92; N, 5.53); tlc (ethyl acetate) Rf 0.56.

4-[2-(1,3-Dioxan-2-yl)ethoxy]nitrobenzene (1.52 g; 6.0 mmol) was reduced with hydrazine hydrate (0.900 g; 18.0 mmol) according to Procedure H. 4-[2-(1,3-Dioxan-2-yl)ethoxy]aniline (1.34 g, 100%) was obtained as colourless plates with mp 78-80°C; tlc (ethyl acetate) Rf 0.42.

4-Chloroquinazoline (0.165 g; 1.0 mmol) and 4-[2-(1,3-dioxan-2-yl)ethoxy]aniline (0.279 g; 1.25 mmol) were reacted in 2-propanol (5 ml) for 45 minutes according to Procedure B. The product was thus obtained as yellow plates (0.361 g, 93%) with mp 209-211°C (effervesc.); (Found C, 61.98; H, 5.72; N, 10.82. $C_{20}H_{21}N_3O_3.HCl$ requires C, 61.93; H, 5.68; N, 10.84); tlc (ethyl acetate) Rf 0.33; δH [$^2H_6$]-DMSO 11.62 (1H, br s, NH), 8.91 (1H, d, J 8, 8-H), 8.85 (1H, s, 2-H), 8.04-8.13 (1H, m, 7-H), 7.98 (1H, d, J 8, 5-H), 7.84 (1H, t, J 8, 6-H), 7.62 (2H, d, J 9, 2'-H, 6'-H), 7.04 (2H, J 9, 3'-H, 5'-H), 4.71-4.79 (1H, m, 2'"-H), 3.98-4.12 (4H, m, 4'"-H_2, 6'"-H_2), 3.75 (2H, t, J 11, 1"-H_2), 1.81-2.04 (3H, m, 2"-H, 5'"-H_2), 1.38 (1H, d, J 10, 2"-H); m/z (%) 351 (100, M+), 236 (100).

Example 170

6,7-Dimethoxy-4-[4-(1,3-dioxan-2-ylethoxy)anilino]quinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.135 g; 0.6 mmol) and 4-[2-(1,3-dioxan-2-yl)ethoxy]aniline (0.167 g; 0.75 mmol) were reacted in 2-propanol (3 ml) for 75 minutes according to Procedure B. The product was thus obtained as a bright yellow solid (0.263 g, 98%) with mp 246-247°C (effervesc.); (Found C, 58.37; H, 6.10; N, 8.91. $C_{22}H_{25}N_3O_5.HCl.0.25H_2O$ requires C, 58.40; H, 5.97; N, 9.29); tlc (ethyl acetate) Rf 0.16; δH [$^2H_6$]-DMSO 11.14 (1H, br s, NH), 8.78 (1H, s, 2-H), 8.31 (1H, s, 8-H), 7.60 (2H, d, J 9, 2'-H, 6'-H), 7.39 (1H, s, 5-H), 7.05 (2H, d, J 9, 3'-H, 5'-H), 4.79 (1H, m, 2'''-H), 3.99-4.16 (4H, m, 4'''-H_2, 6'''-H_2), 4.03 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3), 3.71-3.83 (2H, m, 1''-H_2), 1.86-2.03 (3H, m, 2''-H, 5''-H_2), 1.48 (1H, d, J 10, 2''-H); m/z (%) 411 (100, M+), 296 (100).

Example 171

6-Bromo-4'-[4-(1,3-dioxan-2-ylethoxy) anilino]quinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.146 g; 0.6 mmol) and 4-[2-(1,3-dioxan-2-yl)ethoxy]aniline (0.167 g; 0.75 mmol) were reacted in 2-propanol (3 ml) for 60 minutes according to Procedure B. The product was thus obtained as bright yellow needles (0.243 g; 89%) with mp 211-213°C (effervesc.); (Found C, 51.37; H, 4.65; N, 8.85. $C_{20}H_{20}BrN_3O_3.HCl$ requires C, 51.44; H, 4.50; N, 9.00); tlc (ethyl acetate) Rf 0.43; δ H [$^2H_6$]-DMSO 11.31 (1H, br s, NH), 9.18 (1H, s, 5-H), 8.85 (1H, s, 2-H), 8.20 (1H, d, J 9, 7-H), 7.90 (1H, d, J 9, 8-H), 7.56 (2H, d, J 9, 2'-H, 6'-H), 7.05 (2H, d, J 9, 3'-H, 5'-H), 4.75 (1H, m, 2'''-H), 3.95-4.10 (4H, m, 4'''-H_2, 6'''-H_2), 3.67-3.81 (2H, m, 1''-H_2), 1.85-2.07 (3H, m, 2''-H, 5''-H_2), 1.40 (1H, d, J 10, 2''-H); m/z (%) 431, 429 (100, M+), 316 (93).

Example 172

4-[4-(2-Bromobenzyloxy)-3-chloroanilino]quinazoline hydrochloride

2-Chloro-4-nitrophenol (Lancaster) (3.50 g; 20.0 mmol), sodium hydride (0.530 g; 22 mmol), potassium iodide (1 g) and 2-bromobenzyl chloride (Fairfield Chemicals) (4.53 g; 22 mmol) were reacted in dimethylformamide (50 ml) at 45°C for hours according to Procedure F. 4-(2-Bromobenzyloxy)-3-chloronitrobenzene was thus obtained as a pale cream powder (6.69 g, 98%) with mp 135-136°C; (Found C, 44.21; H, 2.58; N, 3.76. $C_{13}H_9BrClNO_3.0.5H_2O$ requires C, 44.38; H, 2.84; N, 3.98); tlc (ethyl acetate) Rf 0.75.

4-(2-Bromobenzyloxy)-3-chloronitrobenzene (1.48 g; 4.25 mmol) was reduced with hydrazine hydrate (0.638 g; 12.75 mmol) according to Procedure H. 4-(2-Bromobenzyloxy)-3-chloro aniline (1.33 g, 100%) was obtained as colourless prisms

with mp 84-85°C; (Found C, 49.61; H, 3.66; N, 4.21. $C_{13}H_{11}BrClNO$ requires C, 49.92; H, 3.52; N, 4.48); tlc (ethyl acetate) Rf 0.63.

4-Chloroquinazoline (0.164 g; 1.0 mmol) and 4-(2-bromobenzyloxy)-3-chloroaniline (0.390 g; 1.25 mmol) were reacted in 2-propanol (7 ml) for 30 minutes according to Procedure B. The product was thus obtained as fine bright yellow needles (0.433 g, 91%) with mp 240-242°C; (Found C, 52.39; H, 3.99; N, 7.98. $C_{21}H_{15}BrClN_3O.HCl.0.5H_2O.0.67i$-PrOH requires C, 52.47; H, 4.24; N, 7.98); tlc (ethyl acetate) Rf 0.45; δH [$^2H_6$]-DMSO 11.62 (1H, br s, NH), 8.95 (2H, s, 2-H, 8-H), 8.10-8.18 (1H, m, 7-H), 7.95-8.03 (2H, m, 2'-H, 6'-H), 7.84-7.91 (1H, m, 5-H), 7.64-7.76 (3H, m, 6-H, 3"-H, 6"-H), 7.47 (1H, t, J 9, 5"-H), 7.30-7.41 (2H, m, 5'-H, 4"-H), 5.31 (2H, s, CH_2); m/z (%) 441 (86, M+), 270 (100).

Example 173

4-[4-(2-Bromobenzyloxy)-3-chloroanilino]-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.135 g; 0.60 mmol) and 4-(2-bromobenzyloxy)-3-chloroaniline (0.234 g; 0.75 mmol) were reacted in 2-propanol (4.5 ml) for 60 minutes according to Procedure B. The product was thus obtained as very pale yellow needles (0.308 g, 96%) with mp 258-259°C; (Found C, 51.33; H, 3.75; N, 7.91. $C_{23}H_{19}BrClN_3O_3.HCl$ requires C, 51.39; H, 3.72; N, 7.82); tlc (ethyl acetate) Rf 0.30; δH [$^2H_6$]-DMSO 11.61 (1H, br s, NH), 8.73 (1H, s, 2-H), 8.34 (1H, s, 8-H), 7.93 (1H, s, 5H), 7.63-7.78 (3H, m, 2'-H, 6'-H, 6"-H), 7.30-7.51 (4H, m, 5'-H, 3"-H, 4"-H, 5"-H), 5.30 (2H, s, CH_2), 4.06 and 4.01 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 501 (18, M+), 330 (100).

Example 174

4-[4-(2-Bromobenzyloxy)-3-chloro]anilino-6,7-diethoxyquinazoline hydrochloride

4-Chloro-6,7-diethoxyquinazoline (0.063 g; 0.25 mmol) and 4-(2-bromobenzyloxy)-3-chloroaniline (0.100 g; 0.32 mmol) were reacted in 2-propanol (2 ml) for 30 minutes according to Procedure B. The product was thus obtained as pale yellow prisms (0.106 g, 75%) with mp 278-280°C (effervesc.); (Found C, 52.94; H, 4.19; N, 7.35. $C_{25}H_{23}BrClN_3O_3.HCl$ requires C, 53.10; H, 4.25; N, 7.43); tlc (ethyl acetate) Rf 0.43; δH [$^2H_6$]-DMSO 11.44 (1H, br s, NH), 8.79 (1H, s, 2-H), 8.23 (1H, s, 8-H), 7.89 (1H, s, 5-H), 7.62-7.75 (3H, m, 2'-H, 6'-H, 6"-H), 7.50 (2H, t, J 9, 4"-H, 5"-H), 7.30-7.41 (2H, m, 5'-H, 3"-H), 5.29 (2H, s, CH_2), 4.29 (4H, t, J 7, 2 x OCH_2), 1.48 (6H, t, J 7, 2 x CH_3); m/z (%) 529 (11, M+), 358 (100).

Example 175

6-Bromo-4-[4-(2-bromobenzyloxy)-3-chloroanilino]quinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.146 g; 0.60 mmol) and 4-(2-bromobenzyloxy)-3-chloroaniline (0.234 g; 0.75 mmol) were reacted in 2-propanol (4.5 ml) for 60 minutes according to Procedure B. The product was thus obtained as yellow prisms (0.315 g, 95%) with mp 260-261°C; (Found C, 45.48; H, 2.72; N, 7.55. $C_{21}H_{14}Br_2ClN_3O.HCl$ requires C, 45.32; H, 2.70; N, 7.55); tlc (ethyl acetate) Rf 0.57; δH [$^2H_6$]-DMSO 11.47 (1H, br s, NH), 9.26 (1H, s, 5-H), 8.95 (1H, s, 2-H), 8.25 (1H, d, J 9, 7-H), 7.91-8.02 (2H, m, 8-H, 6"-H), 7.62-7.77 (3H, m, 2'-H, 6'-H, 3"-H), 7.33-7.53 (3H, m, 5'-H, 4"-H, 5"-H), 5.29 (2H, s, CH_2); m/z (%) 519 (22, M+), 350 (100), 169 (48).

Example 176

4-[4-(2-Fluorobenzyloxy)-2-methylanilino]quinazoline hydrochloride

3-Methyl-4-nitrophenol (Aldrich) (4.0 g; 26.1 mmol), sodium hydride (0.710 g; 28.7 mmol), potassium iodide (1 g) and 2-fluorobenzyl bromide (Aldrich) (5.18 g; 27.4 mmol) were reacted in dimethylformamide (70 ml) at 60°C for 1.5 hours according to Procedure F. 5-(2-Fluorobenzyloxy)-2-nitrotoluene was thus obtained as a beige solid (6.58 g, 97%) with mp 90-92°C; (Found C, 64.04; H, 4.61; N, 5.08. $C_{14}H_{12}FNO_3$ requires C, 64.37; H, 4.60; N, 5.36); tlc (ethyl acetate) Rf 0.73.

5-(2-Fluorobenzyloxy)-2-nitrotoluene (0.339 g; 1.3 mmol) was reduced with hydrazine hydrate (0.195 g; 3.9 mmol) according to Procedure H. 4-(2-Fluorobenzyloxy)-2-methylaniline (0.300g, 100%) was obtained as a colourless oil; tlc (ethyl acetate-cyclohexane, 4:1) Rf 0.48.

4-Chloroquinazoline (0.082 g; 0.50 mmol) and 4-(2-fluorobenzyloxy)-2-methylaniline (0.150 g; 0.65 mmol) were reacted in 2-propanol (6 ml) for 10 hours acording to Procedure B. The product was thus obtained as a colourless solid (0.182 g, 91%) with mp 275-277°C; (Found C, 65.88; H, 4.85; N, 10.35. $C_{22}H_{18}FN_3O.HCl.0.25H_2O$ requires C, 66.00; H, 4.85; N, 10.50); tlc (ethyl acetate) Rf 0.36; δH [$^2H_6$]-DMSO 11.33 (1H, br s, NH), 8.80 (2H, m, 2-H, 8-H), 8.11 (1H, m, 7-H), 7.98 (1H, m, 5-H), 7.87 (1H, m, 6-H), 7.60 (1H, m, 4"-H), 7.46 (1H, m, 5"-H), 7.30 (3H, m, 6'-H, 3"-H, 6"-H), 7.10 (1H, s, 3'-H), 6.99 (1H, d, J 9, 5'-H), 5.20 (2H, s, CH_2), 2.21 (3H, s, 2'-CH_3); m/z (%) 359 (24, M+), 250 (100).

Example 177

6,7-Dimethoxy-4-[4-(2-fluorobenzyloxy)-2-methyl]anilinoquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.112 g; 0.50 mmol) and 4-(2-fluorobenzyloxy)-2-methylaniline (0.150 g; 0.65 mmol) were reacted in 2-propanol (6 ml) for 5 hours according to Procedure B. The product was thus obtained as a colourless solid (0.190 g,

83%) with mp 238-240°C; (Found C, 62.80; H, 4.98; N, 9.13. $C_{24}H_{22}FN_3O_3$.HCl requires C, 63.23; H, 5.08; N, 9.22); tlc (ethyl acetate) Rf 0.24; δH [$^2H_6$]-DMSO 11.36 (1H, br s, NH), 8.60 (1H, s, 2-H), 8.08 (1H, s, 8-H), 7.60 (1H, t, J 7, 4"-H), 7.47 (1H, t, J 7, 5"-H), 6.92-7.41 (6H, m, 5-H, 3'-H, 5'-H, 6'-H, 3"-H, 6"-H), 5.20 (2H, s, CH_2), 4.02 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3), 2.17 (3H, s, 2'-CH_3); m/z (%) 419 (50, M+), 310 (100).

Example 178

6-Bromo-4-[4-(2-fluorobenzyloxy)-2-methyl]anilinoquinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.122 g; 0.50 mmol) and 4-(2-fluorobenzyloxy)-2-methyl aniline (0.150 g; 0.65 mmol) were reacted in 2-propanol (6 ml) for 20 hours according to Procedure B. The product was thus obtained as colourless crystals (0.204 g, 86%) with mp 269-271°C; (Found C, 55.25; H, 3.85; N, 8.66. $C_{22}H_{17}BrFN_3O$.HCl requires C, 55.65; H, 3.79; N, 8.85); tlc (ethyl acetate) Rf 0.47; δH [$^2H_6$]-DMSO 11.23 (1H, br s, NH), 9.08 (1H, s, 5-H), 8.78 (1H, s, 2-H), 8.25 (1H, d, J 9, 7-H), 7.90 (1H, d, J 9, 8-H), 7.61 (1H, t, J 8, 4"-H), 7.46 (1H, m, 5"-H), 7.20-7.30 (3H, m, 6'-H, 3"-H, 6"-H), 7.09 (1H, s, 3'-H), 6.98 (1H, d, J 8, 5'-H), 5.20 (2H, s, CH_2), 2.19 (3H, s, 2'-CH_3); m/z (%) 437, 439 (50, M+), 328 (100).

Example 179

4-[4-(2-Bromobenzyloxy)-3-methoxyanilino]quinazoline hydrochloride

2-Methoxy-4-nitrophenol (Aldrich) (2.0 g; 11.8 mmol), sodium hydride (0.320 g; 13.0 mmol), potassium iodide (0.750 g) and 2-bromobenzyl chloride (Fairfield Chemicals) were reacted in dimethyl formamide (40 ml) at 40°C for 6 hours according to Procedure F. 4-(2-Bromobenzyloxy)-3-methoxynitrobenzene was thus obtained as a pale yellow solid (3.33 g, 99%) with mp 82-84°C; (Found C, 49.45; H, 3.57; N, 3.84. $C_{14}H_{12}BrNO_4$ requires C, 49.72; H, 3.55; N, 4.14); tlc (ethyl acetate) Rf 0.72.

4-(2-Bromobenzyloxy)-3-methoxynitrobenzene (1.22 g; 3.6 mmol) was reduced with hydrazine hydrate (0.542 g; 10.83 mmol) according to Procedure H. 4-(2-Bromobenzyloxy)-3-methoxyaniline (1.10 g, 99%) was obtained as colourless plates with mp 80-82°C; tlc (ethyl acetate) Rf 0.49.

4-Chloroquinazoline (0.082 g; 0.50 mmol) and 4-(2-bromobenzyloxy)-3-methoxyaniline (0.185 g; 0.60 mmol) were reacted in 2-propanol (6 ml) for 3.5 hours according to Procedure B. The product was thus obtained as a pale yellow solid (0.200 g, 83%) with mp 260-262°C; (Found C, 54.66; H, 4.02; N, 8.81. $C_{22}H_{18}BrN_3O_2$.HCl.0.5H_2O requires C, 54.84; H, 4.15; N, 8.72); tlc (ethyl acetate) Rf 0.37; δH [$^2H_6$]-DMSO 11.48 (1H, br s, NH), 8.88 (1H, s, 2-H), 8.83 (1H, d, J 9, 8-H), 8.11 (1H, t, J 8, 7-H), 7.97 (1H,

d, J 9, 5-H), 7.85 (1H, t, J 8, 6-H), 7.70 (1H, d, J 8, 2'-H), 7.61 (1H, d, J 8, 3"-H) 7.26-7.50 (4H, m, 6'-H, 4"-H, 5"-H, 6"-H), 7.12 (1H, d, J 9, 5'-H), 5.18 (2H, s, CH_2), 3.80 (3H, s, 3'-OCH_3); m/z (%) 437, 435 (30, M+), 266 (100).

Example 180

4-[4-(2-Bromobenzyloxy)-3-methoxyanilino]-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.112 g; 0.50 mmol) and 4-(2-bromobenzyloxy)-3-methoxyaniline (0.185 g; 0.60 mmol) were reacted in 2-propanol (6 ml) for 4.5 hours according to Procedure B. The product was thus obtained as a pale yellow solid (0.264 g, 97%) with mp 260-262°C; (Found C, 53.19; H, 4.43; N, 7.75. $C_{24}H_{22}BrN_3O_4.HCl.0.5H_2O$ requires C, 53.19; H, 4.43; N, 7.76); tlc (ethyl acetate) Rf 0.37; δH [$^2H_6$]-DMSO 10.83 (1H, br s, NH), 8.71 (1H, s, 2-H), 8.10 (1H, s, 8-H), 7.68 (1H, d, J 9, 2'-H), 7.60 (1H, d, J 9, 3"-H), 7.04-7.46 (6H, m, 5-H, 5'-H, 6'-H, 4"-H, 5"-H, 6"-H), 5.16 (2H, s, CH_2), 3.98 (6H, s, 6-OCH_3, 7-OCH_3), 3.80 (3H, s, 3'-OCH_3); m/z (%) 495, 497 (15, M+), 326 (100).

Example 181

4-[4-(2-Bromobenzyloxy)-3-methoxy]anilino-6,7-diethoxyquinazoline hydrochloride

4-Chloro-6,7-diethoxyquinazoline (0.076 g; 0.30 mmol) and 4-(2-bromobenzyloxy)-3-methoxyaniline (0.092 g; 0.30 mmol) were reacted in 2-propanol (3 ml) for 45 minutes according to Procedure B. The product was thus obtained as bright yellow prisms (0.143 g, 85%) with mp 267-268°C (effervesc.); (Found C, 53.61; H, 5.62; N, 6.87. $C_{26}H_{26}BrN_3O_4.HCl.0.5i\text{-}PrOH.1.5H_2O$ requires C, 53.44; H, 5.50; N, 6.80); tlc (10% methanol/ethyl acetate) Rf 0.46; δH [$^2H_6$]-DMSO 11.09 (1H, br s, NH), 8.74 (1H, s, 2-H), 8.20 (1H, s, 8-H), 7.70 and 7.61 (2 x 1H, 2 x d, J 9, 3"-H, 6"-H), 7.48 (1H, t, J 8, 5"-H), 7.30-7.40 (3H, m, 5-H, 2'-H, 4"-H), 7.22 and 7.14 (2 x 1H, 2 x d, J 9, 5'-H, 6'-H), 5.17 (2H, s, CH_2), 4.20-4.37 (4H, m, 2 x OCH_2), 3.81 (3H, s, OCH_3), 1.41-1.50 (6H, m, 2 x CH_3); m/z (%) 524, 526 (100, M+1$^+$), 354 (100).

Example 182

6-Bromo-4-[4-(2-bromobenzyloxy)-3-methoxyanilino]quinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.122 g; 0.50 mmol) and 4-(2-bromobenzyloxy)-3-methoxyaniline (0.185 g; 0.60 mmol) were reacted in 2-propanol (6 ml) for 4 hours according to Procedure B. The product was thus obtained as a yellow solid (0.266 g; 96%) with mp 267-270°C; (Found C, 47.34; H, 3.28; N, 7.35. $C_{22}H_{17}Br_2N_3O_2.HCl.0.25H_2O$ requires C, 47.49; H, 3.33; N, 7.56); tlc (ethyl acetate) Rf 0.47; δH [$^2H_6$]-DMSO 10.91 (1H, br s, NH), 8.87 (1H, s, 5-H), 8.62 (1H, s, 2-H),

7.95 (1H, d, J 9, 7-H), 7.62 (1H, d, J 9, 8-H), 7.48 (1H, d, J 8, 2'-H), 7.39 (1H, d, J 8, 3"-H), 7.03-7.26 (4H, m, 6'-H, 4"-H, 5"-H, 6"-H), 6.90 (1H, d, J 9, 5'-H), 4.90 (2H, s, CH_2), 3.57 (3H, s, 3'-OCH_3); m/z (%) 515 (20, M+), 513, 517 (10, M+), 344, 346 (100).

Example 183

4-[3-Chloro-4-(2,4-dichlorophenoxy)anilino]quinazoline hydrochloride

3-Chloro-4-(2,4-dichlorophenoxy)nitrobenzene (Maybridge) (1.50 g; 4.71 mmol) was reduced with hydrazine hydrate (0.710 g; 14.13 mmol) according to Procedure H. 3-Chloro-4-(2,4-dichlorophenoxy)aniline (1.35 g, 99%) was obtained as a fawn solid with mp 87-89°C; (Found C, 50.08; H, 2.90; N, 4.80. $C_{12}H_8Cl_3NO$ requires C, 49.91; H, 2.77; N, 4.85); tlc (ethyl acetate) Rf 0.59.

4-Chloroquinazoline (0.099 g; 0.60 mmol) and 3-chloro-4-(2,4-dichlorophenoxy)aniline (0.202 g; 0.70 mmol) were reacted in 2-propanol (4 ml) for 2 hours according to Procedure B. The product was thus obtained as a cream solid (0.264 g, 97%) with mp 255-258°C; (Found C, 52.83; H, 2.83; N, 9.14. $C_{20}H_{12}Cl_3N_3O.HCl$ requires C, 52.98; H, 2.87; N, 9.27); tlc (ethyl acetate) Rf 0.48; δH [$^2H_6$]-DMSO 11.80 (1H, br s, NH), 9.12 (1H, s, 2-H), 9.08 (1H, d, J 9, 8-H), 7.88-8.34 (6H, m, 5-H, 6-H, 7-H, 2'-H, 6'-H, 3"-H) 7.62 (1H, d, J 9, 5"-H), 7.31 (1H, d, J 8, 5'-H), 7.21 (1H, d, J 8, 6"-H); m/z (%) 416 (100, M+).

Example 184

4-[3-Chloro-4-(2,4-dichlorophenoxy)anilino]-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.135 g; 0.60 mmol) and 3-chloro-4-(2,4-dichlorophenoxy)aniline (0.202 g; 0.70 mmol) were reacted in 2-propanol (4 ml) for 2 hours according to Procedure B. The product was thus obtained as a pale yellow solid (0.282 g, 92%) with mp 269-272°C; (Found C, 51.28; H, 3.19; N, 8.25. $C_{22}H_{16}Cl_3N_3O_3.HCl$ requires C, 51.46; H, 3.31; N, 8.19); tlc (ethyl acetate) Rf 0.26; δ H [$^2H_6$]-DMSO 11.30 (1H, br s, NH), 8.70 (1H, s, 2-H), 8.30 (1H, s, 8-H), 8.10 (1H, s, 7-H), 7.68-7.80 (2H, m, 2'-H, 6'-H), 7.44 (1H, m, 5"-H), 7.35 (1H, s, 3"-H), 7.17 (1H, d, J 8, 5'-H), 7.04 (1H, d, J 8, 6"-H), 4.03 and 4.00 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 475 (100, M+).

Example 185

6-Bromo-4-[3-chloro-4-(2,4-dichlorophenoxy)anilino]quinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.146 g; 0.60 mmol) and 3-chloro-4-(2,4-dichlorophenoxy) aniline (0.202 g; 0.70 mmol) were reacted in 2-propanol (4 ml) for 2.5 hours according to Procedure B. The product was thus obtained as a pale yellow solid

(0.296 g, 93%) with mp 244-247°C; (Found C, 45.21; H, 2.25; N, 7.82. $C_{20}H_{11}BrCl_3N_3O.HCl$ requires C, 45.12; H, 2.26; N, 7.90); tlc (ethyl acetate) Rf 0.61; δH [$^2H_6$]-DMSO 11.42 (1H, br s, NH), 9.20 (1H, s, 5-H), 8.91 (1H, s, 2-H), 8.10-8.27 (2H, m, 7-H, 8-H), 7.70-7.98 (3H, m, 2'-H, 6'-H, 3"-H), 7.44 (1H, d, J 9, 5"-H), 7.67 (1H, d, J 8, 3'-H), 7.56 (1H, d, J 8, 6"-H); m/z (%) 495 (100, M+).

Example 186

4-[3-Chloro-4-(2-fluorobenzyloxy)anilino]quinazoline hydrochloride

2-Chloro-4-nitrophenol (Lancaster) (1.75 g; 10 mmol), sodium hydride (0.265 g; 11 mmol), potassium iodide (0.500 g) and 2-fluorobenzyl bromide (Aldrich) (2.08 g; 11 mmol) were reacted in dimethylformamide (25 ml) at 55°C for 4.5 hours according to Procedure F. 3-Chloro-4-(2-fluorobenzyloxy)nitrobenzene was thus obtained as a pale yellow solid (2.80 g, 100%) with mp 120-121°C; (Found C, 55.57; H, 3.33; N, 4.94. $C_{13}H_9ClFNO_3$ requires C, 55.42; H, 3.20; N, 4.97); tlc (ethyl acetate) Rf 0.67.

3-Chloro-4-(2-fluorobenzyloxy)nitrobenzene (1.41 g; 5.0 mmol) was reduced with hydrazine hydrate (0.750 g; 15.0 mmol) according to Procedure H. 3-Chloro-4-(2-fluoro-benzyloxy)aniline (1.26 g, 100%) was obtained as pale silver plates with mp 75-76°C; (Found C, 61.69; H, 4.63; N, 5.55. $C_{13}H_{12}ClFNO$ requires C, 61.80; H, 4.76; N, 5.56); tlc (ethyl acetate) Rf 0.56.

4-Chloroquinazoline (0.165 g; 1.0 mmol) and 3-chloro-4-(2-fluorobenzyloxy)aniline (0.316 g; 1.25 mmol) were reacted in 2-propanol (7.5 ml) for 40 minutes according to Procedure B. The product was thus obtained as bright yellow needles (0.383 g; 92%) with mp 224-225°C; (Found C, 60.41; H, 3.83; N, 9.96. $C_{21}H_{15}ClFN_3O.HCl$ requires C, 60.57; H, 3.84;.N, 10.09); tlc (ethyl acetate) Rf 0.13, (10% methanol/ethyl acetate) Rf 0.55; δH [$^2H_6$]-DMSO 11.62 (1H, br s, NH), 8.95 (2H, m, 2-H, 8-H), 8.13 (1H, m, 7-H), 7.82-8.07 (3H, m, 5-H, 2'-H, 6'-H), 7.59-7.78 (2H, m, 6-H, 5"-H), 7.40-7.51 (2H, m, 3"-H, 4"-H), 7.23-7.32 (2H, m, 5'-H, 6"-H), 5.30 (2H, s, CH_2); m/z (%) 379 (19, M+), 270 (100).

Example 187

4-[3-Chloro-4-(2-fluorobenzyloxy)anilino]-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.135 g; 0.60 mmol) and 3-chloro-4-(2-fluorobenxyloxy)aniline (0.189 g; 0.75 mmol) were reacted in 2-propanol (4.5 ml) for 50 minutes according to Procedure B. The product was thus obtained as pale yellow prisms (0.278 g; 97%) with mp 261-262°C; (Found C, 56.98; H, 4.17; N, 8.59. $C_{23}H_{19}ClFN_3O_3.HCl.0.5H_2O$ requires C, 56.90; H, 4.32; N, 8.66); tlc (10% methanol/ethyl acetate) Rf 0.47; δH [$^2H_6$]-DMSO 11.49 (1H, br s, NH), 8.81 (1H, s, 2-

H), 8.37 (1H, s, 8-H), 7.92 (1H, s, 5-H), 7.58-7.72 (2H, m, 2'-H, 6'-H), 7.22-7.47 (5H, m, 5'-H, 3"-H, 4"-H, 5"-H, 6"-H), 5.31 (2H, s, CH_2), 4.10 and 4.04 (2 x 3H, 2 x s, 2 x OCH_3); m/z (%) 439 (22, M+), 330 (100).

Example 188

4-[3-Chloro-4-(2-fluorobenzyloxy)]anilino-6,7-diethoxyquinazoline hydrochloride

4-Chloro-6,7-diethoxyquinazoline (0.076 g; 0.30 mmol) and 3-chloro-4-(2-fluorobenzyloxy)aniline (0.089 g; 0.35 mmol) were reacted in 2-propanol (2.5 ml) for 30 minutes according to Procedure B. The product was thus obtained as a pale yellow prisms (0.116 g, 77%) with mp 267-268°C (dec.); (Found C, 59.25; H, 4.75; N, 8.27. $C_{25}H_{23}ClFN_3O_3.HCl$ requires C, 59.52; H, 4.76; N, 8.33); tlc (ethyl acetate) Rf 0.41; δ H [$^2H_6$]-DMSO 11.63 (1H, br s, NH), 8.80 (1H, s, 2-H), 8.28 (1H, s, 8-H), 7.88 (1H, s, 5-H), 7.58-7.70 (2H, m, 2'-H, 6'-H), 7.20-7.51 (5H, m, 5'-H, 3"-H, 4"-H, 5"-H, 6"H), 5.31 (2H, s, CH_2), 4.20-4.36 (4H, m, 2 x OCH_2), 1.40-1.51 (6H, m, 2 x CH_3); m/z (%) 467 (15, M+), 358 (100).

Example 189

6-Bromo-4-[3-chloro-4-(2-fluorobenzyloxy)anilino]quinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.146 g; 0.60 mmol) and 3-chloro-4-(2-fluorobenzyloxy)aniline (0.189 g; 0.75 mmol) were reacted in 2-propanol (4.5 ml) for 45 minutes according to Procedure B. The product was thus obtained as bright yellow prisms (0.249 g, 84%) with mp 253-254°C; (Found C, 50.80; H, 3.03; N, 8.38. $C_{21}H_{14}BrClFN_3O.HCl$ requires C, 50.91; H, 3.03; N, 8.48); tlc (10% methanol in ethyl acetate) Rf 0.62; δH [$^2H_6$]-DMSO 11.42 (1H, br s, NH), 9.19 (1H, s, 5-H), 8.91 (1H, s, 2-H), 8.20 (1H, d, J 9, 7-H), 7.97 (1H, s, 2'-H), 7.92 (1H, d, J 9, 6'-H), 7.73 (1H, d, J 8, 8-H), 7.61 (1H, m, 4"-H), 7.21-7.51 (4H, m, 5'-H, 3"-H, 5"-H, 6"-H), 5.31 (2H, s, CH_2); m/z (%) 459 (19, M+), 350 (100).

Example 190

4-[4-(2,6-Dichlorobenzyloxy)-3-methoxyanilino]quinazoline hydrochloride

2-Methoxy-4-nitrophenol (Aldrich) (2.54 g; 15 mmol), sodium hydride (0.396 g; 16.5 mmol) and 2,6-dichlorobenzyl chloride (Aldrich) (3.89 g; 15.75 mmol) were reacted in dimethyl-formamide (45 ml) at 80°C for 5 hours according to Procedure E. 4-(2,6-Dichlorobenzyloxy)-3-methoxynitrobenzene was thus obtained as a pale yellow powder (4.83 g; 98%) with mp 174-177°C; (Found C, 51.79; H, 3.35; N, 4.27. $C_{14}H_{11}Cl_2NO_4$ requires C, 51.22; H, 3.35; N, 4.28), tlc (ethyl acetate) Rf 0.68.

4-(2,6-Dichlorobenzyloxy)-3-methoxynitrobenzene (1.28 g; 3.9 mmol) was reduced with hydrazine hydrate (0.586 g; 11.7 mmol) according to Procedure H. 4-(2,6-Dichloro-benzyloxy)-3-methoxyaniline (1.09 g, 94%) was thus obtained as colourless needles with mp 114-115°C; tlc (ethyl acetate) Rf 0.62.

4-Chloroquinazoline (0.082 g; 0.50 mmol) and 4-(2,6-dichlorobenzyloxy)-3-methoxyaniline (0.180 g; 0.60 mmol) were reacted in 2-propanol (4 ml) for 2.5 hours according to Procedure B. The product was thus obtained as a yellow solid (0.203 g, 88%) with mp 263-265°C; (Found C, 56.98; H. 3.94; N, 8.77. $C_{22}H_{17}Cl_2N_3O_2.HCl$ requires C, 57.10; H, 3.70; N, 9.08); tlc (ethyl acetate) Rf 0.46; δH [$^2H_6$]-DMSO 11.44 (1H, br s, NH), 8.87 (1H, s, 2-H), 8.83 (1H, s, 8-H), 8.10 (1H, t, J 8, 7-H), 7.96 (1H, d, J 9, 5-H), 7.84 (1H, t, J 8, 6-H), 7.30-7.61 (5H, m, 2'-H, 6'-H, 3"-H, 4"-H, 5"-H), 7.25 (1H, d, J 9, 5'-H), 5.26 (2H, s, CH_2), 3.78 (3H, s, 3'-OCH_3); m/z (%) 425 (6, M+), 266 (100).

Example 191

4-[4-(2,6-Dichlorobenzyloxy)-3-methoxyanilino]-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.112 g; 0.50 mmol) and 4-(2,6-dichlorobenzyloxy)-3-methoxyaniline (0.180 g; 0.60 mmol) were reacted in 2-propanol (4 ml) for 2.5 hours according to Procedure B. The product was thus obtained as a yellow solid (0.220 g, 83%) with mp 263-265°C; (Found C, 54.69; H, 4.08; N, 7.98. $C_{24}H_{21}Cl_2N_3O_4.HCl.0.25H_2O$ requires C, 54.64; H, 4.27; N, 7.97); tlc (ethyl acetate) Rf 0.19; δH [$^2H_6$]-DMSO 10.82 (1H, br s, NH), 8.70 (1H, s, 2-H), 8.13 (1H, s, 8-H), 7.42-7.58 (3H, m, 2'-H, 6'-H, 4"-H), 7.16-7.47 (4H, m, 5-H, 5'-H, 3"-H, 5"-H), 5.29 (2H, s, CH_2), 4.02 and 4.00 (2 x 3H, 2 x s, 6-OCH_3, 7-OCH_3), 3.76 (3H, s, 3'-OCH_3); m/z (%) 486 (95, M+1), 326 (100).

Example 192

4-[4-(2,6-Dichlorobenzyloxy)-3-methoxyanilino]-6,7-diethoxyquinazoline hydrochloride

4-Chloro-6,7-diethoxyquinazoline (0.126 g; 0.50 mmol) and 4-(2,6-dichloro benzyloxy)-3-methoxyaniline (0.180 g; 0.60 mmol) were reacted in 2-propanol (5 ml) for 3 hours according to Procedure B. The product was thus obtained as a pale yellow solid (0.253 g, 92%) with mp 273-275°C; (Found C, 56.14; H, 4.68; N, 7.45. $C_{26}H_{25}Cl_2N_3O_4.HCl$ requires C, 56.68; H, 4.72; N, 7.63); tlc (ethyl acetate) Rf 0.27; δ H [$^2H_6$]-DMSO 11.17 (1H, br s, NH), 8.94 (1H, s, 2-H), 8.33 (1H, s, 8-H), 7.63-7.79 (3H, m, 2'-H, 6'-H, 4"-H), 7.39-7.55 (4H, m, 5-H, 5'-H, 3"-H, 5"-H), 5.48 (2H, s, CH_2),

4.43-4.53 (4H, m, 2 x OCH_2), 3.96 (3H, s, OCH_3), 1.64 (6H, t, J 7, 2 x CH_3); m/z (%) 513 (14, M+), 354 (100).

Example 193

6-Bromo-4-[4-(2,6-dichlorobenzyloxy)-3-methoxy]anilinoquinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.122 g; 0.50 mmol) and 4-(2,6-dichlorobenzyloxy)-3-methoxyaniline (0.149 g; 0.50 mmol) were reacted in 2-propanol (3 ml) for 30 minutes according to Procedure B. The product was thus obtained as bright yellow prisms (0.260 g, 96%) with mp 278-280°C; (Found C, 48.67; H, 3.44; N, 7.62. $C_{22}H_{16}BrCl_2N_3O_2.HCl.$ $0.25H_2O$ requires C, 48.35; H, 3.21; N, 7.69); tlc (ethyl acetate) Rf 0.55; δH [$^2H_6$]-DMSO 11.32 (1H, br s, NH), 9.13 (1H, s, 5-H), 8.90 (1H, s, 2-H), 8.20 (1H, d, J 8, 7-H), 7.88 (1H, d, J 8, 8-H), 7.57 (2H, d, J 9, 3"-H, 5"-H), 7.33-7.53 (3H, m, 2'-H, 6'-H, 4"-H), 7.24 (1H, d, J 9, 5'-H), 5.30 (2H, s, CH_2), 3.81 (3H, s, 3'-OCH_3); m/z (%) 505 (12, M+), 346 (100), 344 (100).

Example 194

4-[4-(2,6-Difluorobenzyloxy)-3-methoxyanilino]quinazoline hydrochloride

2-Methoxy-4-nitrophenol (2.54 g; 15 mmol), sodium hydride (0.396 g; 16.5 mmol) and 2,6-difluorobenzyl chloride (TCI) (3.36 g; 15.75 mmol) were reacted in dimethylformamide (45 ml) at 90°C for 15 hours according to Procedure E. 4-(2,6-Difluorobenzyloxy)-3-methoxynitrobenzene was thus obtained as a pale yellow solid (4.42 g; 100%) with mp 128-130°C; (Found C, 56.92; H, 3.85; N, 4.71. $C_{14}H_{11}F_2NO_4$ requires C, 56.95; H, 3.73; N, 4.75); tlc (ethyl acetate) Rf 0.65.

4-(2,6-Difluorobenzyloxy)-3-methoxynitrobenzene (1.15 g; 3.90 mmol) was reduced with hydrazine hydrate (0.586 g; 11.7 mmol) according to Procedure H. 4-(2,6-Difluorobenzyloxy)-3-methoxyaniline (1.02 g, 99%) was obtained as colourless plates with mp 99-101°C; tlc (ethyl acetate) Rf 0.51.

4-Chloroquinazoline (0.082 g; 0.50 mmol) and 4-(2,6-difluorobenzyloxy)-3-methoxyaniline (0.172 g; 0.65 mmol) were reacted in 2-propanol (5 ml) for 3 hours according to Procedure B. The product was thus obtained as a yellow solid (0.180 g, 84%) with mp 253-256°C; (Found C, 61.55; H, 3.98; N, 9.59. $C_{22}H_{17}F_2N_3O_2.HCl$ requires C, 61.47; H, 4.19; N, 9.78); tlc (ethyl acetate) Rf 0.45; δH [$^2H_6$]-DMSO 11.38 (1H, br s, NH), 8.89 (1H, s, 2-H), 8.80 (1H, d, J 9, 8-H), 8.10 (1H, t, J 8, 7-H), 7.92 (1H, d, J 9, 5-H), 7.87 (1H, t, J 8, 6-H), 7.49-7.59 (1H, m, 4"-H), 7.43 (1H, s, 2'-H), 7.33 (1H, d, J 9, 6'-H), 7.13-7.22 (3H, m, 5'-H, 3"-H, 5"-H), 5.17 (2H, s, CH_2), 3.29 (3H, s, 3'-OCH_3); m/z (%) 394 (100, $M+1^+$), 266 (75).

Example 195

4-[4-(2,6-Difluorobenzyloxy)-3-methoxyanilino]-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.056 g; 0.25 mmol) and 4-(2,6-difluorobenzyloxy)-3-methoxyaniline (0.080 g; 0.30 mmol) were reacted in 2-propanol (2 ml) for 3 hours. The product was thus obtained as a yellow solid (0.112 g, 92%) with mp 259-261°C; (Found C, 58.06; 4.45; N, 8.37. $C_{24}H_{21}F_2N_3O_4.HCl.0.33H_2O$ requires C, 58.12; H, 4.57; N, 8.47); tlc (ethyl acetate) Rf 0.26; δH [$^2H_6$]-DMSO 11.18 (1H, br s, NH), 8.80 (1H, s, 2-H), 8.25 (1H, s, 8-H), 7.50-7.59 (1H, m, 4"-H), 7.32-7.39 (2H, m, 2'-H, 6'-H), 7.15-7.28 (4H, m, 5-H, 5'-H, 3"-H, 5"-H), 5.18 (2H, s, CH_2), 4.02 and 4.00 (2 x 3H, 2 x s, 6-OCH_3, 7-OCH_3), 3.29 (3H, s, 3'-OCH_3); m/z (%) 453 (20, M+), 326 (100).

Example 196

6,7-Diethoxy-4-[4-(2,6-difluorobenzyloxy)-3-methoxyanilino]quinazoline hydrochloride

4-Chloro-6,7-diethoxyquinazoline (0.126 g; 0.50 mmol) and 4-(2,6-difluorobenzyloxy)-3-methoxyaniline (0.172 g; 0.65 mmol) were reacted in 2-propanol (5 ml) for 7 hours according to Procedure B. The product was thus obtained as a pale yellow solid (0.247 g, 93%) with mp 258-259°C; (Found C, 58.97; H, 5.00; N, 7.92. $C_{26}H_{25}F_2N_3O_4.HCl.0.75H_2O$ requires C, 58.75; H, 5.17; N, 7.90); tlc (ethyl acetate) Rf 0.30; δH [$^2H_6$]-DMSO 10.83 (1H, br s, NH), 8.59 (1H, s, 2-H), 8.00 (1H, s, 8-H), 7.31-7.41 (1H, m, 4"-H), 7.12-7.19 (2H, m, 2'-H, 6'-H), 6.97-7.08 (4H, m, 5-H, 5'-H, 3"-H, 5"-H), 4.98 (2H, s, CH_2), 4.05-4.16 (4H, m, 2 x OCH_2), 3.60 (3H, s, 3'-OCH_3), 1.28 (6H, t, J 8, 2 x CH_3); m/z (%) 481 (8, M+), 354 (100).

Example 197

6-Bromo-4-[4-(2,6-difluorobenzyloxy)-3-methoxyanilino]quinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.122 g; 0.50 mmol) and 4-(2,6-difluorobenzyloxy)-3-methoxyaniline (0.133 g; 0.50 mmol) were reacted in 2-propanol (3 ml) for 35 minutes according to Procedure B. The product was thus obtained as bright yellow prisms (0.244 g, 95%) with mp 243-245°C (dec.); (Found C, 51.59; H, 3.68; N, 8.17. $C_{22}H_{16}BrF_2N_3O_2$. $HCl.0.25H_2O$ requires C, 51.46; H, 3.41; N, 8.18); tlc (5% methanol/ethyl acetate) Rf 0.52; δH [$^2H_6$]-DMSO 11.20 (1H, br, NH), 9.08 (1H, s, 5-H), 8.88 (1H, s, 2-H), 8.19 (1H, d, J 9, 7-H), 7.88 (1H, d, J 9, 8-H), 7.50-7.60 (1H, m, 4"-H), 7.18-7.48 (5H, m, 2'-H, 5'-H, 6'-H, 3"-H, 5"-H), 5.16 (2H, s, CH_2), 3.79 (3H, s, 3'-OCH_3); m/z (%) 473, 471 (32, M+1$^+$), 344 (100).

Example 198

4-[3-Methoxy-4-(2-methoxybenzyloxy)]anilinoquinazoline hydrochloride

2-Methoxy-4-nitrophenol (Aldrich) (3.38 g; 20.0 mmol), sodium hydride (0.530 g; 22.0 mmol), potassium iodide (1.0 g) and 2-methoxybenzylchloride (Transworld) (3.12 g; 21.0 mmol) were reacted in dimethylformamide (50 ml) at 60°C for 4.5 hours according to Procedure F. 3-Methoxy-4-(2-methoxybenzyloxy)nitrobenzene was thus obtained as a cream solid (3.39 g, 61%) with mp 87-88°C; (Found C, 62.32; H, 5.31; N, 4.67. $C_{15}H_{15}NO_5$ requires C, 62.28; H, 5.19; N, 4.84); tlc (ethyl acetate) Rf 0.72.

3-Methoxy-4-(2-methoxybenzyloxy)nitrobenzene (1.88 g; 6.5 mmol) was reduced with hydrazine hydrate (0.976 g; 19.5 mmol) according to Procedure H. 3-Methoxy-4-(2-methoxy-benzyloxy)aniline (1.62 g, 96%) was obtained as air-sensitive colourless needles with mp 80-81°C; (Found C, 69.71; H, 6.59; N, 5.01. $C_{15}H_{17}NO_3$ requires C, 69.50; H, 6.56; N, 5.40); tlc (ethyl acetate) Rf 0.50.

4-Chloroquinazoline (0.099 g; 0.60 mmol) and 3-methoxy-4-(2-methoxybenzyloxy)aniline (0.181 g; 0.70 mmol) were reacted in 2-propanol (3 ml) for 20 minutes according to Procedure B. The product was thus obtained as pale yellow plates (0.206 g, 81%) with mp 199-201°C; (Found C, 63.25; H, 5.40; N, 9.43. $C_{23}H_{21}N_3O_3.HCl.0.75H_2O$ requires C, 63.15; H, 5.38; N, 9.61); δH [$^2H_6$]-DMSO 11.50 (1H, br s, NH), 8.87 (1H, s, 2-H), 8.82 (1H, d, J 9, 8-H), 8.10 (1H, t, J 8, 7-H), 7.94 (1H, d, J 9, 5-H), 7.85 (1H, t, J 8, 6-H), 7.25-7.47 (4H, m, 2'-H, 6'-H, 4"-H, 6"-H), 6.91-7.14 (3H, m, 5'-H, 3"-H, 5"-H), 5.11 (2H, s, CH_2), 3.88 and 3.80 (2 x 3H, 2 x s, 3'-OCH_3, 2"-OCH_3); m/z (%) 387 (32, M+), 266 (100).

Example 199

6,7-Dimethoxy-4-[3-methoxy-4-(2-methoxybenzyloxy)]anilinoquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.135 g; 0.60 mmol) and 3-methoxy-4-(2-methoxybenzyloxy)aniline (0.181 g; 0.70 mmol) were reacted in 2-propanol (3 ml) for 40 minutes according to Procedure B. The product was thus obtained as lemon-yellow prisms (0.284 g, 98%) with mp 250-252°C; (Found C, 61.62; H, 5.34; N, 8.38. $C_{25}H_{25}N_3O_5$. $HCl.0.25H_2O$ requires C, 61.47; H, 5.43; N, 8.60); δH [$^2H_6$]-DMSO 10.94 (1H, br s, NH), 8.71 (1H, s, 2-H), 8.15 (1H, s, 8-H), 6.92-7.47 (8H, m, 5-H, 2'-H, 5'-H, 6'-H, 3"-H, 4"-H, 5"-H, 6"-H), 5.10 (2H, s, CH_2), 4.02 and 3.98 (2 x 3H, 2 x s, 6-OCH_3, 7-OCH_3), 3.85 and 3.80 (2 x 3H, 2 x s, 3'-OCH_3, 2"-OCH_3); m/z (%) 447 (16, M+), 326 (100).

Example 200

6,7-Diethoxy-4-[3-methoxy-4-(2-methoxybenzyloxy)]anilinoquinazoline hydrochloride

4-Chloro-6,7-diethoxyquinazoline (0.152 g; 0.60 mmol) and 3-methoxy-4-(2-methoxybenzyloxy)aniline (0.181 g; 0.70 mmol) were reacted in 2-propanol (3 ml) for 30 minutes according to Procedure B. The product was thus obtained as yellow prisms (0.304 g, 99%) with mp 244-245°C; (Found C, 63.02; H, 5.80; N, 7.96. $C_{27}H_{29}N_3O_5.HCl$ requires C, 63.34; H, 5.86; N, 8.21); tlc (5% methanol/ethyl acetate) Rf 0.52; δH [$^2H_6$]-DMSO 11.11 (1H, br s, NH), 8.73 (1H, s, 2-H), 8.20 (1H, s, 8-H), 7.29 (4H, m, 5-H, 2'-H, 6'-H, 4"-H), 6.96-7.22 (4H, m, 5'-H, 3"-H. 5"-H, 6"-H), 5.10 (2H, s, CH_2), 4.20-4.35 (4H, m, 2 x OCH_2), 3.88 and 3.81 (2 x 3H, 2 x s, 3'-OCH_3, 2"-OCH_3), 1.38-1.50 (6H, m, 2 x CH_3); m/z (%) 475 (18, M+), 354 (100).

Example 201

6-Bromo-4-[3-methoxy-4-(2-methoxybenzyloxy)]anilinoquinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.146 g; 0.60 mmol) and 3-methoxy-4-(2-methoxybenzyloxy) aniline (0.181 g; 0.7 mmol) were reacted in 2-propanol (3 ml) for 40 minutes according to Procedure B. The product was thus obtained as bright yellow prisms (0.276 g, 92%) with mp 215-217°C; (Found C, 54.70; H, 4.21; N, 8.05. $C_{23}H_{20}BrN_3O_3.HCl$ requires C, 54.93; H, 4.18; N, 8.36); tlc (ethyl acetate) Rf 0.51; δ H [$^2H_6$]-DMSO 11.47 (1H, br s, NH), 9.19 (1H, s, 5-H), 8.89 (1H, s. 2-H), 8.20 (1H, d, J 9, 7-H), 7.90 (1H, d, J 9, 8-H), 7.30-7.48 (4H, m, 2'-H, 6'-H, 4"-H, 6"-H), 7.03-7.13 (2H, m, 5'-H, 3"-H), 6.99 (1H, t, J 8, 5"-H), 5.10 (2H, s, CH_2), 3.82 and 3.20 (2 x 3H, 2 x s, 3'-OCH_3, 2"-OCH_3); m/z (%) 467, 465 (49, M+), 344, 346 (90). 121 (100).

Example 202

4-[3-Chloro-4-(2-methoxybenzyloxy)]anilinoquinazoline hydrochloride

2-Chloro-4-nitrophenol (3.50 g; 20.0 mmol), sodium hydride (0.530 g; 22.0 mmol) and potassium iodide (1.0 g) were reacted in dimethylformamide (50 ml) at 40°C for 6.5 hours according to Procedure F. 3-Chloro-4-(2-methoxybenzyloxy)nitrobenzene was thus obtained as a mustard yellow solid (5.24 g; 89%) with mp 100-101°C; (Found C, 57.20; H, 4.11; N, 4.67. $C_{14}H_{12}ClNO_4$ requires C, 57.24; H, 4.09; N, 4.77); tlc (ethyl acetate) Rf 0.69.

3-Chloro-4-(2-methoxybenzyloxy)nitrobenzene (1.98 g; 6.75 mmol) was reduced with hydrazine hydrate (1.01 g; 20.25 mmol) according to Procedure H. 3-Chloro-4-(2-methoxybenzyloxy)aniline (1.63 g, 98%) was obtained as an almost colourless oil; tlc (ethyl acetate) Rf 0.52.

4-Chloroquinazoline (0.099 g; 0.60 mmol) and 3-chloro-4-(2-methoxybenzyloxy)aniline (0.161 g; 0.65 mmol) were reacted in 2-propanol (4 ml) for 25 minutes according to Procedure B. The product was thus obtained as pale lemon yellow prisms (0.220 g; 86%) with mp 222-224°C; (Found C, 61.15; H, 5.52; N, 8.49. $C_{22}H_{18}ClN_3O_2$.HCl.*i*-PrOH.0.25H_2O requires C, 60.91; H, 5.58; N, 8.52); tlc (ethyl acetate Rf 0.50; δH [$^2H_6$]-DMSO 11.66 (1H, br s, NH), 8.92 (2H, m, 2-H, 8-H), 8.12 (1H, t, J 7, 7-H), 8.00 (1H, d, J 8, 5-H), 7.93 (1H, s, 2'-H), 7.86 (1H, t, J 7, 6-H), 7.69 (1H, d, J 9, 6'-H), 7.49 (1H, d, J 9, 6"-H), 7.29-7.40 (2H, m, 3"-H, 4"-H), 7.10 (1H, d, J 9, 5'-H), 7.00 (1H, t, J 7, 5"-H), 5.23 (2H, s, CH_2), 3.89 (3H, s, 2"-OCH_3); m/z (%) 391 (49, M+), 270 (42).

Example 203

4-[3-Chloro-4-(2-methoxybenzyloxy)]anilino-6,7-dimethoxyquinazoline hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (0.135 g; 0.60 mmol) and 3-chloro-4-(2-methoxybenzyloxy)aniline (0.161 g; 0.65 mmol) were reacted in 2-propanol (4 ml) for 45 minutes according to Procedure B. The product was thus obtained as pale lemon yellow prisms (0.291 g, 99%) with mp 237-239°C; (Found C, 58.95; H, 4.80; N, 8.42. $C_{24}H_{22}ClN_3O_4$.HCl requires C, 59.01; H, 4.71; N, 8.60); tlc (ethyl acetate) Rf 0.33; δ H [$^2H_6$]-DMSO 11.41 (1H, br s, NH), 9.30 (1H, s, 2-H), 8.37 (1H, s, 8-H), 7.89 (1H, s, 2'-H), 7.68 (1H, d, J 9, 6'-H), 7.45 (1H, s, 5-H), 7.30-7.41 (3H, m, 3"-H, 4"-H, 6"-H), 7.09 (1H, d, J 9, 5'-H), 7.00 (1H, t, J 8, 5"-H), 5.21 (2H, s, CH_2), 4.03 and 4.00 (2 x 3H, 2 x s, 6-OCH_3, 7-OCH_3), 3.38 (3H, s, 2"-OCH_3); m/z (%) 451 (37, M+), 330 (47).

Example 204

4-[3-Chloro-4-(2-methoxy benzyloxy)]anilino-6,7-diethoxyquinazoline hydrochloride

4-Chloro-6,7-diethoxyquinazoline (0.152 g; 0.60 mmol) and 3-chloro-4-(2-methoxybenzyloxy)aniline (0.161 g; 0.65 mmol) were reacted in 2-propanol (4 ml) for 40 minutes according to Procedure B. The product was thus obtained as pale yellow prisms (0.277 g, 90%) with mp 252-253°C; (Found C, 60.26; H, 5.14; N, 8.03. $C_{26}H_{26}ClN_3O_4$.HCl requires C, 60.47; H, 5.23; N, 8.14); tlc (ethyl acetate) Rf 0.44; δ H [$^2H_6$]-DMSO 11.30 (1H, br s, NH), 8.79 (1H, s, 2-H), 8.29 (1H, s, 8-H), 7.87 (1H, s, 2'-H), 7.64 (1H, d, J 9, 6'-H), 7.46 (1H, d, J 9, 6"-H), 7.24-7.40 (3H, m, 5-H, 3"-H, 4"-H), 6.93-7.11 (2H, m, 5'-H, 5"-H), 5.21 (2H, s, CH_2), 4.20-4.36 (4H, m, 2 x OCH_2), 3.87 (3H, s, 2"-OCH_3), 1.40-1.52 (6H, m, 2 x CH_3); m/z (%) 479 (16, M+).

Example 205

4-[3-Chloro-4-(2-methoxybenzyloxy)anilino]-6,7-methylenedioxyquinazoline hydrochloride

4-Chloro-6,7-methylenedioxyquinazoline (0.113 g; 0.50 mmol) and 3-chloro-4-(2-methoxybenzyloxy)aniline (0.145 g; 0.55 mmol) were reacted in 2-propanol (3.5 ml) for 55 minutes according to Procedure B. The product was thus obtained as a pale beige solid (0.225 g, 95%) with mp 260-262°C (effervesc.); (Found C, 58.28; H, 4.11; N, 8.75. $C_{23}H_{18}ClN_3O_4.HCl$ requires C, 58.47; H, 4.02; N, 8.90); tlc (ethyl acetate) Rf 0.50; δH [$^2H_6$]-DMSO 10.83 (1H, br s, NH), 8.79 (1H, s, 2-H), 8.24 (1H, s, 8-H), 7.90 (1H, s, 2'-H), 7.61 (1H, d, J 9, 6'-H), 7.48 (1H, d, J 9, 6"-H), 7.22-7.40 (3H, m, 5-H, 3"-H, 4"-H), 7.00-7.10 (2H, m, 5'-H, 5"-H), 6.38 (2H, s, CH_2O_2), 5.23 (2H, s, CH_2), 3.87 (3H, s, 2"-OCH_3); m/z (%) 436 (100, $M+1^+$).

Example 206

6-Bromo-4-[3-chloro-4-(2-methoxybenzyloxy)]anilinoquinazoline hydrochloride

6-Bromo-4-chloroquinazoline (0.146 g; 0.60 mmol) and 3-chloro-4-(2-methoxybenzyloxy)aniline (0.161 g; 0.65 mmol) were reacted in 2-propanol (4 ml) for 40 minutes according to Procedure B. The product was thus obtained as bright yellow prisms (0.283 g; 93%) with mp 224-226°C; (Found C, 52.24; H, 3.69; N, 8.00. $C_{22}H_{17}BrClN_3O_2.HCl$ requires C, 52.07; H, 3.55; N. 8.28); tlc (ethyl acetate) Rf 0.61; δH [$^2H_6$]-DMSO 11.39 (1H, br s, NH), 9.15 (1H, s, 5-H), 8.89 (1H, s, 2-H), 8.19 (1H, d, J 9, 7-H), 7.36-7.95 (2H, m, 8-H, 2'-H), 7.68 (1H, d, J 9, 6'-H), 7.46 (1H, d, J 9, 6"-H), 7.29-7.39 (2H, m, 3"-H, 4"-H), 7.10 (1H, d, J 9, 5'-H), 6.99 (1H, t, J 7, 5"-H), 5.32 (2H, s, CH_2), 3.37 (3H, s, 2"-OCH_3); m/z (%) 471 (11, M+), 350 (15).

Biological Data

Compounds of the present invention were tested for protein tyrosine kinase inhibitory activity in a substrate phosphorylation assay and an autophosphorylation assay. The results are shown in Table 1 below as the IC_{50} values in μm.

The substrate phosphorylation assay uses a baculovirus expressed, recombinant construct of the intracellular domain of c-erbB-2 that is constitutively active. The method measures the ability of the isolated enzyme to catalyse the transfer of ^{33}P-labelled γ-phosphate from ATP onto tyrosine residues in a synthetic peptide.

The enzyme is incubated for 1 hour, at room temperature, with 100μM ATP, 10mM $MnCl_2$, 1mg/ml PolyGluAlaTyr (6:3:1) and test compound (diluted from a 5mM stock in DMSO, final DMSO concentration is 2%) in 40mM HEPES buffer, pH 7.4. The reaction is stopped by the addition of EDTA (final concentration 0.1M) and the peptide is then precipitated onto ion exchange filter paper and the incorporated radioactivity

determined. Inhibition of the c-erbB-2 kinase is compared routinely against EGF-R TK activity, measured in the same assay method, using solubilised A431 membranes as a source of enzyme activity.

The erbB-2 autophosphorylation ELISA assay measures the level of phosphorylation on the receptor itself in intact cells following exposure to test compound (Developed from the method of King et al, Life Sci, (1993) Vol 53, pp1465-1472). It uses an immortalised, primary human breast epithelial cell line (HB4a C5.2) which has been transfected with human c-erbB-2 and expresses high levels of constitutively phosphorylated kinase in its plasma membrane.
The cells are exposed to test compound for 2 hours in multiwell plates, washed and then lysed with ice-cold buffer containing 20mM TRIS, pH 8.0, 137mM NaCl, 10% (w/v) glycerol, 1% (w/v) Nonidet P-40, 1mM phenylmethylsulphonyl fluoride, 20µg/ml aprotinin and 1mM sodium vanadate. The lysates are transferred to 96-well ELISA plates which have been coated with an anti-erbB-2 antibody and subsequently blocked with a 3% milk solution. After 60 minutes incubation at 37°C, the lysates are washed from the wells and the phosphotyrosine on the captured receptor is detected using a biotinylated anti-phosphotyrosine antibody/Horse radish peroxidase-conjugated anti-biotin antibody system. The EGFR autophosphorylation assay uses the same method and is performed using A431 cells and an anti-EGFR antibody-coated ELISA plate.

Table 1

	Substrate Phosphorylation		Autophosphorylation	
Example	EGFR	c-erbB-2	EGFR	c-erbB-2
3	>50	0.94	31	1.3
6	>50	10	>50	2.2
7	>50	1.6	>50	3.1
9	50	1.7	>50	9.8
12	>50	1.6	>50	2.5
23	8	0.021	c30	0.28
24	>50	8.4	c50	21
25	45	0.18	17	0.19
26	5	0.057	c50	0.32
27	>30	3.5	>50	4.5
29	11	0.31	28	0.25
30	15	0.050	12	0.23
33	65	0.38	>50	2.4
42	>30	0.68	c50	2.3
48	10	0.080	29	0.45
58	>50	0.23	>50	0.72
89	15	0.38	>50	1.3
120	1.6	0.09	6.9	0.68
143	>50	0.32	>50	1.3

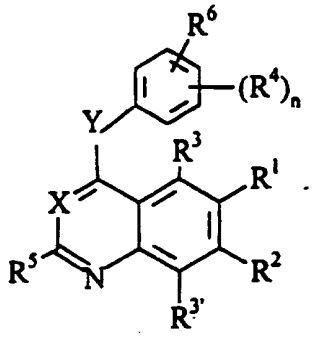
Table 2 illustrates the inhibitory activity of compounds of the present invention against p56lck protein tyrosine kinase. The results are presented as the IC_{50} values in μm. The assay is identical to the c-erbB-2 assay except that c-erbB-2 is replaced by p56lck protein.

Table 2

Example	p56lck
3	5
4	1.9
23	0.5
81	3
83	10

Claims

1) A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein X is N or CH;

Y is a group $W(CH_2)$, $(CH_2)W$, or W, in which W is O, $S(O)_m$ wherein m is 0, 1 or 2, or NR^a wherein R^a is hydrogen or a C_{1-8} alkyl group;

R^1, R^2, R^3 and $R^{3'}$ are the same or different and are each selected from the group comprising; amino, hydrogen, halogen, hydroxy, nitro, carboxy, trifluoromethyl, trifluoromethoxy, carbamoyl, ureido, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-8} cycloalkoxyl, C_{4-8} alkylcyclo alkoxy, C_{1-8} alkoxycarbonyl, N-C_{1-4} alkylcarbamoyl, N,N-di-[C_{1-4} alkyl]carbamoyl, hydroxyamino, C_{1-4} alkoxyamino, C_{2-4} alkanoyloxyamino, C_{1-4} alkylamino, di[C_{1-4} alkyl]amino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-C_{1-4} alkylpiperazin-1-yl, C_{1-8} alkylthio, arylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, arylsulphonyl, halogeno-C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{2-4} alkanoyloxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4} alkyl, carboxy-C_{1-4} alkyl, C_{1-4} alkoxycarbonyl-C_{1-4}-alkyl,carbamoyl-C_{1-4} alkyl, N-C_{1-4} alkylcarbamoyl-C_{1-4}alkyl, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4}alkyl, amino-C_{1-4} alkyl, C_{1-4} alkylamino-C_{1-4} alkyl, di-[C_{1-4} alkyl]amino-C_{1-4} alkyl, piperidino-C_{1-4} alkyl, morpholino-C_{1-4} alkyl, piperazin-1-yl-C_{1-4} alkyl, 4-C_{1-4} alkylpiperazin-1-yl-C_{1-4} alkyl, hydroxy-C_{2-4} alkoxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkoxy-C_{1-4} alkyl, hydroxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkylthio-C_{1-4} alkyl, hydroxy-C_{2-4} alkylthio-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylthio-C_{1-4} alkyl, phenoxy-C_{1-4} alkyl, anilino-C_{1-4} alkyl, phenylthio-C_{1-4}

alkyl, cyano-C_{1-4} alkyl, halogeno-C_{2-4} alkoxy, hydroxy-C_{2-4} alkoxy, C_{2-4} alkanoyloxy-C_{2-4} alkoxy, C_{1-4} alkoxy-C_{2-4} alkoxy, carboxy-C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl-C_{1-4} alkoxy, carbamoyl-C_{1-4} alkoxy, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkoxy, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkoxy, amino-C_{2-4} alkoxy, C_{1-4} alkylamino-C_{2-4} alkoxy, di-[C_{1-4} alkyl]amino-C_{2-4} alkoxy, C_{2-4} alkanoyloxy, hydroxy-C_{2-4} alkanoyloxy, C_{1-4}alkoxy-C_{2-4} alkanoyloxy, phenyl-C_{1-4} alkoxy, phenoxy-C_{2-4} alkoxy, anilino-C_{2-4} alkoxy, phenylthio-C_{2-4} alkoxy, piperidino-C_{2-4} alkoxy, morpholino-C_{2-4} alkoxy, piperazin-1-yl-C_{2-4} alkoxy, 4-C_{1-4} alkylpiperazin-1-yl-C_{2-4} alkoxy, halogeno-C_{2-4} alkylamino, hydroxy-C_{2-4} alkylamino, C_{2-4} alkanoyloxy-C_{2-4} alkylamino, C_{1-4} alkoxy-C_{2-4} alkylamino, carboxy-C_{1-4} alkylamino, C_{1-4} alkoxycarbonyl-C_{1-4} alkylamino, carbamoyl-C_{1-4} alkylamino, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkylamino, amino-C_{2-4} alkylamino, C_{1-4} alkylamino-C_{2-4} alkylamino, di-[C_{1-4}alkylamino-C_{2-4} alkylamino, phenyl-C_{1-4} alkylamino, phenoxy-C_{2-4} alkylamino, anilino-C_{2-4} alkylamino, phenylthio-C_{2-4} alkylamino, C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonylamino, C_{1-4} alkylsulphonylamino, benzamido, benzenesulphonamido, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, halogeno-C_{2-4} alkanoylamino, hydroxy-C_{2-4} alkanoylamino, C_{1-4} alkoxy-C_{2-4} alkanoylamino, carboxy-C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonyl-C_{2-4} alkanoylamino, carbamoyl-C_{2-4} alkanoylamino, N-C_{1-4} alkylcarbamoyl-C_{2-4} alkanoylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{2-4} alkanoylamino, amino-C_{2-4} alkanoylamino, C_{1-4} alkylamino-C_{2-4} alkanoylamino and di-[C_{1-4} alkyl]amino-C_{2-4} alkanoylamino, and wherein said benzamido or benzenesulphonamido substitutent or any anilino, phenoxy or phenyl group on a R^1 substituent may optionally bear one or two halogeno, C_{1-4} alkyl or C_{1-4} alkoxy substituents;

or R^1 and R^2, R^1 and R^3, or R^2 and $R^{3'}$ together form an optionally substituted methylenedioxy or ethylenedioxy group;

each R^4 is independently selected from the group comprising; hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino, di-[C_{1-4} alkyl]amino, C_{1-4} alkylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbamoyl, di-[C_{1-4} alkyl] carbamoyl, carbamyl, C_{1-4} alkoxycarbonyl, cyano, nitro and trifluoromethyl, and n is 1,2 or 3;

R^5 is selected from the group comprising; hydrogen, halogen, trifluoromethyl, C_{1-4} alkyl or C_{1-4} alkoxy;

R^6 is a group ZR^7 wherein Z is joined to R^7 through a $(CH_2)p$ group in which p is 0, 1 or 2 and Z represents a group $V(CH_2)$, $V(CF_2)$, $(CH_2)V$, $(CF_2)V$ or V in which V is a hydrocarbyl group containing 0,1 or 2 carbon atoms, carbonyl, CH(OH), sulphonamide, amide, O, $S(O)_m$ or NR^b where R^b is hydrogen or R^b is C_{1-4} alkyl;

and R^7 is an optionally substituted C_{3-6} cycloalkyl; or an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety;

or R^6 is a group ZR^7 in which Z is NR^b, and NR^b and R^7 together form an optionally substituted 5, 6, 7, 8, 9 or 10-membered heterocyclic moiety.

2. A compound as claimed in claim 1, wherein R^1, R^2 and R^3 are each selected from amino, hydrogen, halogen, hydroxy, nitro, C_{1-8} alkyl, C_{1-8} alkoxy C_{1-8} alkylthio, C_{1-4} alkylamino, or R^1 and R^2 or R^1 and R^3 together form an optionally substituted methylenedioxy or ethylenedioxy group;
$R^{3'}$ is hydrogen; R^4 is hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, di-[C_{1-4} alkyl]amino nitro or trifluoromethyl;
R^5 is hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy;
Z is oxygen, S or NR^b wherein R^b is hydrogen, or C_{1-4} alkyl, and
R^7 is an optionally substituted 5, 6, 7, 8, 9 or 10 membered- carbocyclic
or heterocyclic moiety

3. A compound as claimed in claim 2, wherein R^1, R^2 and R^3 are each selected from; hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy or together form a methylenedioxy or ethylenedioxy group.

4. A compound as claimed in claim 1, 2 or 3, wherein R^6 is in the para position with respect to Y.

5. A compound as claimed in claim 1, 2, 3, or 4, wherein $(R^4)_n$ represents meta substituent(s) with respect to Y.

6. A compound as claimed in any preceding claim, wherein the substituent which may be optionally present on the phenyl, benzyl, naphthyl or 5,6,7,8,9 or 10-membered carbocyclic or heterocyclic moiety is selected from the group comprising; hydroxy, halogen, trifluoromethyl, trifluoromethoxy, nitro, amino, cyano, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylcarbonyl, carboxylate and C_{1-4} alkoxy carboxyl.

7. A compound as claimed in any preceding claim wherein X is N.

8. A compound as claimed in any preceding claim, wherein Y is NR^b, $NR^b(CH_2)$, or $(CH_2)NR^b$.

9. A compound as claimed in claim 8 wherein Y is NR^b.

10. A compound as claimed in any preceding claim, wherein Z is CH_2, NR^b, $NR^b(CH_2)$, $(CH_2)NR^b$,O, $O(CH_2)$, $O(CF_2)$, $(CH_2)O$, $(CF_2)O$, $S(CH_2)$, or carbonyl.

11. A compound as claimed in claim 10 wherein Z is NR^b or O.

12. A compound as claimed in any preceding claim, wherein the 5, 6, 7, 8, 9 or 10-membered heterocyclic moiety is selected from the group comprising: furan, dioxolane, thiophene, pyrrole, imidazole, pyrrolidine, pyran, pyridine, pyrimidine, morpholine, oxazoline, benzofuran, indole, isoindole, quinazoline, quinoline and isoquinoline.

13. A compound as claimed in any one of claims 1 to 11, wherein the 5, 6, 7, 8, 9 or 10- membered carbocyclic moiety is selected from the group comprising: phenyl, indene, napthalene, tetralin, decalin, cyclopentyl, cyclohexyl, and cycloheptyl.

14. A compound as claimed in claim 12 wherein R^6 is thiophenemethoxy, or in claim 13 wherein R^6 is phenoxy, benzyloxy or cyclohexylmethoxy.

15. A compound as claimed in any preceding claim, wherein each R^4 is hydrogen.

16. A compound as claimed in any preceding claim, wherein R^5 is hydrogen.

17. A compound as claimed in claim 1 selected from the group comprising:
4-(4-Phenoxyanilino)quinoline ;
4-(4-Benzyloxyanilino)quinoline;
4-(4-Benzyloxyanilino)-6,7-dimethoxyquinoline;
5-Chloro-2-[4-(6,7-dimethoxy-4-quinolylamino)-2-methylphenyl]isoindol-1,3-dione;
4-(4-Benzyloxyphenoxy)quinazoline;
6,7-Dimethoxy-4-(4-phenoxyanilino)quinazoline;
4-(3-Benzyloxyanilino)quinazoline;
4-(4-Benzyloxyanilino)quinazoline;
4-(4-Benzyloxyanilino)-6,7-dimethoxyquinazoline;
4-(4-Benzyloxyanilino)-6,7-dimethylquinazoline;
4-(4-Benzyloxyanilino)-5-methoxyquinazoline;
4-(4-Benzyloxyanilino)-6-methoxyquinazoline;
4-(4-Benzyloxyanilino)-7-methoxyquinazoline;
4-(4-Benzyloxyanilino)-7-chloroquinazoline;
4-(4-Benzyloxyanilino)-6-bromoquinazoline;
6-Nitro-4-(4-phenoxyanilino)quinazoline;
4-(4-Anilinoanilino)-6,7-dimethoxyquinazoline;
4-(4-Benzyloxy-3-methoxyanilino)-6,7-dimethoxyquinazoline;
4-[4-(2-Thienylmethoxy)anilino]quinazoline;
and pharmaceutically acceptable salts thereof.

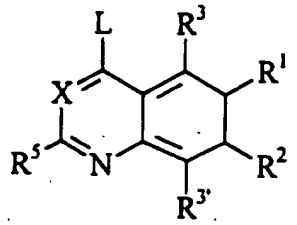
18. A compound as claimed in claim 17 selected from the group comprising:
4-(4-Benzyloxyanilino)quinazoline; and
4-(4-Benzyloxyanilino)-6,7-dimethoxyquinazoline;
and pharmaceutically acceptable salts thereof.

19. Method of treatment of the human or animal body suffering from a disorder mediated by aberrant tyrosine kinase activity which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to the human or animal patient.

20. Pharmaceutical formulation comprising one or more compounds of formula (I), or pharmaceutically acceptable salt(s) thereof, together with one or more pharmaceutically acceptable carriers.

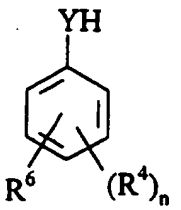
21. A unit dosage form containing a compound of formula (I) or a pharmaceutically acceptable salt thereof in an amount from 70 to 700 mg.

22. Method of making a compound of formula (1), or a pharmaceutically acceptable salt thereof, the method including the step of reacting a compound of formula (II):



(II)

with a compound of formula (III):



(III)

where L is a leaving group and X, Y and R^1 to R^6 are as hereinbefore defined.

23. A method as claimed in claim 22, the method including the step of transforming a compound of formula (I) into another compound of formula (I).

24. A method as claimed in claim 23, wherein the transformation step is the oxidation of an alkyl or aryl mercapto group to a sulphinyl or sulphonyl compound; the reduction of a nitro group to an amine; or the acylation of an amino or hydroxy group.

25. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in therapy.

26. Use of a compound of formula (I) in the preparation of a medicament for the treatment of malignant tumours.

27. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of atherosclerosis, restenosis or thrombosis.

INTERNATIONAL SEARCH REPORT

Interna' al Application No
PCT/GB 95/02202

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/94 C07D239/88 C07D239/95 C07D215/44 C07D409/12
A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,95 15758 (RHONE-POULENC) 15 June 1995 see claims	1,20-27
X	US,A,2 474 823 (J. BURCKHALTER ET AL.) 5 July 1949 see column 1 - column 11; example 8	1,20-27
X	EP,A,0 326 329 (LILLY) 2 August 1989 see page 1 - page 20; claims	1,22
X	EP,A,0 326 328 (LILLY) 2 August 1989 see claims	1,22
X	EP,A,0 326 330 (LILLY) 2 August 1989 see claims	1,22
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

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'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 January 1996	19. 01. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Francois, J

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INTERNATIONAL SEARCH REPORT

Internati ' Application No
PCT/GB 95/02202

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,86 06718 (AUSTRALIAN NAT. UNIVERSITY.) 20 November 1986 see the whole document	1,20-27
X	WO,A,93 03030 (PFIZER) 18 February 1993 see claims; examples 13-59	1,20-27
A	EP,A,0 191 603 (FUJISAWA) 20 August 1986 see claims	1,20-27
A	EP,A,0 370 704 (UBE INDUSTR.) 30 May 1990 see page 7 - page 20; claims; examples 4,13-19	1,20-27
X	CHEMICAL ABSTRACTS, vol. 72, no. 11, 1970, Columbus, Ohio, US; abstract no. 55356n, R. COLLINS ET AL. 'CHEMOTHERAPY OF FASCIOLIASIS.1' page 422 ; see abstract & J. SCI. FOOD AGR., vol.20, no.11, 1969, ENGL. pages 690 - 695	1,20
X	CHEMICAL ABSTRACTS, vol. 92, no. 15, 1980, Columbus, Ohio, US; abstract no. 128687w, V.MISRA ET AL. 'SYNTH. OF NEW SUBSTITUTED QUINOLINES' page 678 ; see abstract & INDIAN J. CHEM. SECT.B, vol.18, no.3, 1979, INDIA pages 262 - 264	1
X	CHEMICAL ABSTRACTS, vol. 95, no. 1, 1981, Columbus, Ohio, US; abstract no. 7199s, AGRAWAL,V. ET AL. 'STUDIES IN POTENTIAL FILARICIDES.PART X1' page 682-683 ; see abstract & INDIAN J. OF CHEM. SECT B, vol.19, no.12, INDIA pages 1084 - 1087	1,20

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INTERNATIONAL SEARCH REPORT

Interna' al Application No
PCT/GB 95/02202

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 105, no. 28, 1986, Columbus, Ohio, US; abstract no. 42720b, ABUZAR,S. ET AL. 'SYNTHESIS OF 2,5(6)-DISUBSTITUTED BENZIMIDAZOLES' page 731 ; see abstract & INDIAN J. CHEM. SECT.B, vol.24, no.8, 1985, INDIA pages 848 - 852 ---	1,20
X	CHEMICAL ABSTRACTS, vol. 105, no. 1, 1986, Columbus, Ohio, US; abstract no. 72286g, BETHEGNIES,G. ET AL. '7-CHLOROPHENYLTHIO-4 -PHENYLAMINOQUINOLINES.' page 37 ; see abstract & FARMACO ED. SCI., vol.41, no.6, 1986, LILLE pages 471 - 477 ---	1,20
X	CHEMICAL ABSTRACTS, vol. 108, no. 27, 1988, Columbus, Ohio, US; abstract no. 186530z, V. AGRAWAL ET AL. 'ANTIPARASITIC AGENTS. PART VI.' page 685 ; see abstract & INDIAN J. CHEM. SECT. B, vol.26, no.6, 1987, INDIA pages 550 - 555 ---	1,20
X	CHEMICAL ABSTRACTS, vol. 118, no. 21, 1993, Columbus, Ohio, US; abstract no. 212849p, MOYER,M. ET AL. 'THE SYNTHESIS AND IDENTIFIC. OF 4,6-DIAMINO-QUINOLINEDERIV. AS POTENT IMMUNOSTIMULANTS.' page 894 ; see abstract & BIOORG. MED. CHEM. LETT., vol.2, no.12, 1992, USA pages 1589 - 1594 -----	1,20-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB95/02202

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 19 is directed to a method of treatment of the human body, the search has been carried out and based on the attributed effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat' l Application No
PCT/GB 95/02202

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9515758	15-06-95	US-A-	5480883	02-01-96
		AU-B-	1305095	27-06-95
US-A-2474823	05-07-49	NONE		
EP-A-0326329	02-08-89	AU-B-	632994	21-01-93
		AU-B-	2874789	03-08-89
		EG-A-	19187	30-10-94
		JP-A-	1226877	11-09-89
		PT-B-	89506	29-04-94
		US-A-	5411963	02-05-95
EP-A-0326328	02-08-89	AU-B-	2874889	03-08-89
		JP-A-	1246264	02-10-89
		US-A-	5296484	22-03-94
EP-A-0326330	02-08-89	AU-B-	2872889	03-08-89
		EG-A-	18859	29-09-94
		FI-B-	94523	15-06-95
		HU-B-	208611	28-12-93
		JP-A-	1246263	02-10-89
		US-A-	5145843	08-09-92
		US-A-	5240940	31-08-93
WO-A-8606718	20-11-86	AU-B-	5954886	04-12-86
		EP-A-	0222839	27-05-87
		JP-T-	63500173	21-01-88
WO-A-9303030	18-02-93	CA-A-	2114727	18-02-93
		EP-A-	0597003	18-05-94
		FI-A-	940469	01-02-94
		JP-T-	6504294	19-05-94
EP-A-0191603	20-08-86	AU-B-	5270786	14-08-86
		JP-A-	61183283	15-08-86
		SU-A-	1450740	07-01-89
		US-A-	4735952	05-04-88
EP-A-0370704	30-05-90	DE-D-	68920963	16-03-95
		DE-T-	68920963	28-09-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 95/02202

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0370704		ES-T-	2066864	16-03-95
		US-A-	5141941	25-08-92
		JP-A-	3163066	15-07-91
		JP-B-	7091277	04-10-95
		JP-A-	3007267	14-01-91
		JP-B-	7051565	05-06-95